THE MODERN TREATMENT OF SYPHILIS

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SYPHILIS

SECOND EDITION 1941

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With

Chapter XXXIII *Intensive Arsenotherapy of Early Syphilis,* completely rewritten

and

Chapter XXXIV *Venereal Disease Control in the Army and Navy* newly introduced

By

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1944

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PREFACE TO THE SECOND EDITION

In the original preface and introductory chapter to this book I acknowledged my indebtedness to past and present members of the staff of the Syphilis Division of the Johns Hopkins University and Hospital. Nearly ten years ago when the first edition was in preparation, my indebtedness was based on the excellent work which these physicians had performed on patients their painstaking and unremitting efforts to keep good records, and their individual published studies of clinical and experimental problems. Almost equal thanks were due and offered to nurses, social workers, and secretaries whose energy had kept patients under long-term observation and who had operated a record system which made clinical material available for analysis The effort of writing the first edition was nevertheless my own.

In this second edition, I must recognize anew my original debt. Now, however I am under much deeper obligation. When the task of revision and addition was undertaken some two years ago I found myself unable, for various reasons, to complete it within any predictable period of time. Rather than abandon the effort (since I feel that there is still a need for a monographic presentation of syphilotherapy) I called upon certain of my associates for more detailed aid. Four of them listed on the title page as collaborators were asked to undertake certain responsibilities which each of them has more than adequately performed, at some sacrifice of personal interests.

Dr Jarold E. Kemp at that time physician-in-charge of the Syphilis Division of the Public Health Institute Chicago and now fortunately re-associated with the Syphilis Division of the Johns Hopkins University and in charge of its program of post-graduate teaching, undertook to revise and bring up to date the entire manuscript. Every chapter has passed through his hands, and he has contributed largely to many of them.

Dr Harry Eagle completely rewrote the present Chapter XXVIII on the interpretation of serologic tests in the diagnosis and treatment of syphilis.

Dr Paul Padget undertook the revision of the present Chapter XVIII on the treatment of cardiovascular syphilis.

Dr Mary Goodwin has completely revised the present Chapters XXVI and XXVII, dealing respectively with the treatment of the syphilitic pregnant woman and the antenatal prevention of congenital syphilis, and with the treatment of congenital syphilis. Newer knowledge in these fields has been advanced by studies many yet unpublished, in our own newly organized Family Clinic in which Dr Goodwin has played an important rôle.

In thus transferring the major part of the labor of this second edition to other shoulders, I have not given up my personal responsibility for the text. First with Dr Kemp and my other collaborators, and later alone, I

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have gone over the entire manuscript, as to facts, opinions and language, and I cheerfully accept entire responsibility for its contents.

Of the 32 chapters in the first edition, 23 have been completely rewritten and brought up to date on the basis of our own experience and the literature. Two of these original chapters have been amalgamated into one. To Chapter III has been added a long and much needed discussion of infectiousness in syphilis and its relation to treatment, for which I am wholly responsible. There are two entirely new chapters, one of which (XXXIII on the intensive arsenotherapy of syphilis) is a joint effort of Kemp, Eagle and myself the other (XXXII on the public health aspects of the treatment of syphilis) is my own.

In order to conserve space, the bibliography is kept at about the same length as in the first edition by the omission of certain older articles there referred to in order to compensate for the addition of many more recent references.

Grateful appreciation is due to Mrs Thomas Parran, who corrected and rearranged Chapter III and to the editors of many medical journals and the authors of numerous articles who have graciously given permission for quotation or the reproduction of certain figures. Credit is of course assigned where necessary in the text.

Finally, though this edition once more appears as Moore's *Modern Treatment of Syphilis*, it might much more appropriately be known by the authorship of Moore and Kemp with the collaboration of Eagle, Padget, and Goodwin. My thanks to each of them!

J. E. M.

August 16 1941

PREFACE TO THE FIRST EDITION

THIS book could not have been brought to completion without the aid and cooperation of many persons. My great indebtedness to the group of physicians now or formerly members of the staff of the Syphilis Division is separately expressed in the introductory chapter as well as through frequent citation of their published work. It is a particular pleasure to offer my grateful appreciation to Dr Albert Keidel, whose skilful organization of the clinic, during his many years as Physician-in-Charge made relatively easy the clinical study of a large number of patients, and whose encouragement and advice have steered me over many difficult shoals to Dr Alan M Chesney who has read the entire manuscript, and whose critical and stimulating comment has been of the utmost aid to Drs. Alan C Woods E. Cowles Andrus Harry Eagle and Ernest L. Zimmermann who have reviewed for me individual chapters dealing with their special interests in ophthalmology cardiology and serology to Max Brödel, who made the splendid drawings illustrating the technique of lumbar and cisterna puncture to Barbara Stouffer and Eleanor Zouck social workers whose success in following patients has made available much clinical material and to my secretary Mason Gieske, whose untiring aid has been invaluable.

I am obligated also to the editors of the Johns Hopkins Hospital Bulletin, the Canadian Medical Association Journal and the Archives of Dermatology and Syphilology for permission to reprint figures which have appeared in their journals and to Dr John H. Stokes for permission to reproduce two figures from certain of his papers.

Finally my thanks are due to my publisher Charles C Thomas, for many helpful suggestions as to the format of the book.

A word as to the bibliography is desirable. I have made no attempt to document every statement in the text, though references covering most controversial points are provided. To supply a complete bibliography would necessitate another volume larger than this one. For the sake of the practitioner who desires further details, and of the deeper student who wishes to consult source materials, I have however made an effort to provide references to most really important points with particular emphasis on recent contributions, and, for the benefit of the English-speaking reader the majority of them are in English. Each chapter has its own bibliography Numbered references are purposely omitted, since they make reading difficult, but when an author is cited in the text the pertinent reference may be located at a glance under his name in the alphabetical arrangement of the several bibliographies.

J.E.M

Baltimore, August 1933

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Chapter I

INTRODUCTION

The modern treatment of syphilis dates from the discoveries of the five-year period 1905–1910 including the demonstration of the causative organism the development of a serologic test now universally known as the Wassermann reaction, and the introduction of salvarsan. Thirty years have elapsed since the last of these, sufficient time to permit an appraisal of accomplishment. That such an appraisal is desirable is apparent from the interest of physicians in the subject. The prevalence of syphilis and the multiplicity of its manifestations make it a matter of concern to the general practitioner and to specialists in every domain of medicine Aided by the routine serologic test and by clinical experience, four-fifths of the physician s difficulties of diagnosis are solved. What to do when the infection has been recognized is, however another matter, especially urgent to the practitioner who treats only the occasional patient. He is entitled to the best available information on the subject, information which at present he can gain only from widely scattered contributions in the periodic literature, from expensive texts which deal with diagnosis and treatment alike, or which provide a mass of minute chemotherapeutic detail unnecessary for practical application, or from the advertising of pharmaceutical houses.

Experts in syphilology are roughly divided into three classes, one of which believes that syphilotherapy is in such a state of flux that no definite statements can be made at present as to preferred methods of treatment one which holds that standardization of treatment for all types of syphilitic infection is not only desirable but at present available and a middle group which takes the position that although present methods are in many respects unsatisfactory new developments constantly occurring, and new methods being introduced, it is nevertheless worth while to describe the best methods of treatment now in use and to relate the attainable results. To this middle group we belong. The discussion of the following chapters is offered, therefore, as a description of current practice and results, with the full knowledge that new discoveries may invalidate completely the work of the past 30 years and that the story is by no means ended. Perfection has not been achieved but, were one to await its advent before attempting a text on the therapy of any disease, one might well postpone indefinitely the task of writing.

A brief description of the material on which this monograph is based is in order The Syphilis Division of the Medical Clinic of the Johns Hopkins Hospital was organized as a separate entity in 1914 under the direction of Keidel. It came into being because of general recognition of the fact that the therapy of syphilis as then practised in a dozen or more separate clinics of a large hospital was utterly unsatisfactory that patients were

being treated by widely varying methods because of individual manifestations of the infection, that such decentralization provided little opportunity for the adequate study of syphilis as a disease problem, and none at all for its social or epidemiologic control. The variety of manifestations of the disease led to the conviction unaltered since, that syphilis is primarily a medical, rather than a urologic dermatologic, ophthalmologic, neurologic or pediatric problem and that the staff of the clinic should be composed of physicians whose training had been primarily in the field of internal medicine, rather than in one of the more restricted specialties. To the clinic were to be referred all patients from any of the hospital services when syphilis was suspected or definitely diagnosed (excepting only infants and young children*). The function of the clinic, in addition to the care of patients was to include teaching and research. The management of the serologic laboratory of the hospital was placed in the hands of the director of the clinic. These original plans have been carried out during the ensuing 27 years and, in addition, provisions were made in 1923 for laboratory research in experimental syphilis under the direction of Chesney, later expanded by the additions of Turner and Eagle.† Thus facilities have been provided for the integration of the study of experimental syphilis in animals, of serologic investigations, and of clinical research. A more complete statement of the desirability of the broadly medical rather than the more highly specialized dermatologic approach to the problems of syphilis (especially as applied to teaching) may be found in Moore's recent discussion of the subject.

*As authors we can claim only to act as spokesmen for a group of physi*cians whose unflagging interest and unremitting efforts have made possible the collection of the clinical data and their study. Numerous publications by members of our staff dealing with laboratory and clinical investigations have appeared in the current literature; these are liberally utilized in the pages which follow. It is impossible to mention by name the many contributors to these studies or to the work of the Syphilis Division; especial acknowledgment is due to Keidel, who was formerly the active chief of the clinic; to Chesney who while in charge of the experimental syphilis laboratories has devoted much valuable thought and effort to the clinic; to some thirty or more physicians (prominent among them Robinson, Wasserman, Halley, Turner, Hopkins and Mohr) whose work has made the clinic possible and whose works are extensively quoted in the following pages; to the support of the several Professors of Medicine under whom the Division has functioned, Barker, Janeway, Thayer, Robinson and Longcope; to the social service workers without whose follow up efforts much of the clinical material would have been valueless; to the nursing and secretarial staff of the clinic whose untiring interest

* Syphilis in infants and children is now also managed by the Syphilis Division, through the organization in 1939 of a Family Clinic in which is centered obstetrical, pediatric, and syphilologic care of pregnant women, mothers and children.

† In addition this second edition is broadened by the inclusion of the clinical and laboratory facilities of the Public Health Institute, Chicago, the Syphilis Division of which was for 6 years under the direction of one of us (J.E.K.)

in the accuracy of the records has given them much of their merit and last, but not least to the individuals and organizations whose financial support has made the conduct of research possible *

We have made extensive use of the contributions of the Cooperative Clinical Group. This group composed of the chiefs of the Syphilis Clinics of the University of Pennsylvania, the Mayo Clinic the University of Michigan, Western Reserve University and Johns Hopkins University (and for a while the Public Health Institute) and of representatives of the United States Public Health Service, has been engaged for several years in retrospective inquiries into the results of treatment in various types of syphilitic infection. The material from all the clinics has been pooled, studied statistically with the aid of the United States Public Health Service, and the conclusions drawn agreed upon by all members of the group. A number of papers have already appeared others, covering other phases of treatment are in process of preparation Several chapters of this monograph are based almost entirely on the studies of the Cooperative Clinical Group (which is designated, for brevity throughout this text as C.C.G.) Many other chapters are based on studies of the material of our own clinic necessitated by its cooperation with the Group

Although this monograph is written largely from the point of view of our own experience it does not neglect the work of other investigators. It makes no pretense of a thorough review of the literature, but the more important contributions are utilized and due credit given in the text and in the bibliographies which follow the several chapters.† If these include a preponderant number of references to the work of our own staff It is hoped that the inclusion is justified on the ground of the character of the text. There are numerous expressions of personal opinion as to the points on which we differ even if only slightly from current opinion or even from other members of our own staff

In general we have attempted to provide information in as simple terms as possible, as to what may be done for patients with various types of syphilis and as to what the physician may expect if he does it. When it seems to us that a particular problem can be handled more properly by the expert, with the clinical background of many syphilitic patients, than by the practitioner who has to deal with only a few we have not hesitated to say so. No apology is necessary for the statistical method of presentation. To attempt to discuss treatment in terms of the individual patient would expand these pages to unreasonable length moreover the best possible answer to the numerous questions of syphilotherapy is a consideration of results in terms of the average member of a large group.

If this monograph supplies a helpful answer even though it be qualified as partial, incomplete and subject to revision on the basis of further ad

* These latter are Mr John D Rockefeller Jr The Interdepartmental Social Hygiene Board, the United States Public Health Service, the Maryland State Department of Health, the Committee on Research in Syphilis, Inc., the Ella Sachs Plotz Foundation, the Milbank Memorial Fund, the American Medical Association, various pharmaceutical houses and numerous anonymous donors.

† Numerous references which appeared in the first edition have been eliminated from this one and newer or more important references added.

vances to the ever recurring question as to how to treat syphilis, its purpose will have been served.

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CHAPTER II

THE BIOLOGY OF SYPHILITIC INFECTION IN RELATION TO TREATMENT

The mode of infection.—The physician who undertakes the treatment of syphilis should have a clear understanding of what happens biologically speaking, to an individual who acquires the disease. Infection usually occurs by direct or indirect contact with moist surfaces, mouth or genitalia, of a recently infected individual. Moisture is a prerequisite for transmission of the virus; the treponeme dies as soon as it dries. It is not known whether the organism can penetrate the unbroken mucous membrane in the human being, or whether a break in its continuity is essential. Since Brown and Pearce have shown that rabbits can be infected by instilling treponemes into the uninjured conjunctival sac, prepuce or vagina, it is probable that the analogous phenomenon may occur in human beings.

The dissemination of the virus.—In experimental animals it has been shown that within a very short time after intratesticular inoculation of the virus (24 hours, Brown and Pearce; 5 minutes, Kolle), treponemes can be demonstrated in the regional lymph nodes. Immediately after inoculation of rabbits they can be recovered from the circulating blood (Raiziss and Severac), indicating their rapid spread both by the blood stream and the lymphatics.* Frazier and Pian report an example of transfusion syphilis from blood supplied by a donor in the incubation period of the disease, thus showing that the same phenomenon occurs in man. Unfortunately the usual method of inoculation (intratesticular) of animals precludes the application of these experimental findings to man. It is possible that the trauma incident to the deposition of an inoculum in the testicle with a needle might not only break down the animal's natural barrier to dissemination of the treponemes but also result in a direct blood stream or lymphatic inoculation. The experiences of Charpy and of Frankl suggest, however, that the behavior of infection in its early stages in man is probably analogous to its early course in experimental animals. Charpy was able to demonstrate treponemes in a completely healed penile abrasion which had occurred during coitus two weeks before. Frankl recovered treponemes from the apparently normal skin of two patients 4 and 6 days respectively after the appearance of the chancre. At least these experiments indicate the futility of attempting to abort syphilis by excision of the primary lesion.

The early tissue reaction of the host.—While the generalized spread of organisms is taking place, there is also occurring a multiplication at the inoculated site, where there appears, after an incubation period ranging from 10 to 90 days but averaging 3 weeks, a characteristic tissue

* According to Stroesco and Valsman dissemination of treponemes in man occurs by way of the connective tissue fibres to the nerves and thence to the spinal ganglia.

reaction known as primary syphilis the chancre Simultaneously or shortly after there appears in most of the cases, a painless rubbery enlargement of the regional lymph nodes the satellite bubo These signs last a few days or weeks and except for residual induration in the bubo heal spontaneously

The blood is not a suitable medium for the growth of treponemes and it is probable that they leave it as soon as possible for the more favorable environment of the tissues Although all tissues of the body are probably equally invaded, lesions do not develop in all. Certain structures and organs chiefly those of ectodermal origin appear to offer more favorable conditions for residence and growth than others Localizing in these specially chosen areas notably skin mucous membranes eye and nervous system, the deposited treponemes undergo a second period of local multiplication which after an average interval of about 6 weeks following the appearance of the chancre culminates in the secondary outbreak, with its diversity of lesions The secondary lesions, as well as the chancre contain large numbers of easily demonstrable organisms and are further characterized by the fact that there is little or no destruction of tissue

These secondary lesions too if the patient is not treated and the course of the infection thereby influenced from without heal spontaneously Depending on their type and intensity they may persist for only a few days or for many months finally to disappear without leaving any permanent scars. It is probable that during the process of healing of the secondary lesions, the treponemes which they contain are in large part destroyed.

The establishment of latency —After the spontaneous healing of the secondary outbreak, there may occur a series of recurring lesions of increasing clinical insignificance and at varying intervals sometimes involving the skin but more often limited to the mucous membranes of mouth or genitalia. These relapsing lesions though often characterized by their very insignificance also contain treponemes in large numbers and are infectious. In some patients they may never appear and in most they cease to occur by the time 3 to 5 years have elapsed. The patient then enters on a period of indeterminate length, varying from a few months to a lifetime but averaging about 7 years, during which there is no outward sign of syphilitic infection, and the presence of the disease is recognizable if at all only by means of serologic tests of the blood. This stage is known as latency

The late tissue reaction of the host —During latency and its apparent quiescence two sets of phenomena may be taking place beneath the outwardly serene surface First, there may be a slowly progressive inflammation mild and exquisitely chronic in various invaded tissues, with subsequent fibrosis. In other individuals a violent inflammatory reaction with marked tissue destruction may suddenly occur in spite of the presence of relatively few organisms This is known as the gumma. The stimulus which provokes this reaction is in a few instances known to be trauma but in most there is no known reason why one patient develops destructive late lesions and another does not nor why they appear

when they do The solution of these two problems is one of the most fascinating will-o the-wisps in syphilology

The late lesions of syphilis, then, may be of two types —the explosive, destructive, allergic reaction of gumma or the physiologic breakdown of important structures, especially cardiovascular or central nervous systems, from the effects of chronic perivascular inflammation and fibrosis The difference is largely one of degree, the essential pathologic lesions being identical.

Symptomless Infection with syphilis —There is one important exception to the biologic course of syphilitic infection so far discussed, namely the complete omission in certain patients of the early lesions of the disease. It has long been common knowledge that many persons with late syphilis (80 per cent or more of all males 60 per cent of all females) could give no history of infection. For this omission there are several possible commonplace reasons.

First, the average patient with syphilis is often thought to be untruthful, an assumption which is certainly unwarranted.

Second, it is well known that in some patients the lesions of early syphilis are wholly insignificant e.g., the trivial fleeting chancre, which resembles an abrasion the hidden cervical chancre in women the transient faint roseola the tiny painless mucosal lesion. These may all be so unimportant as to escape the patient s notice entirely or so similar to more familiar minor clinical phenomena as to be misinterpreted, and in either case to fade promptly from memory That this is often the true explanation for supposedly symptomless infection is repeatedly demonstrated by the physician s discovery of lesions of early syphilis in a patient who had been wholly ignorant of their presence and by the fact that young persons found by routine serologic tests to have latent syphilis can much more frequently supply a story of possible early lesions than can those of an older age group with latent or late syphilis.

Third, it has often been suspected that in males, at least, infection with gonorrhea and syphilis may be simultaneous a painless meatal or urethral chancre being masked by the gonorrheal discharge. Actual evidence as to how often this occurs is conflicting. In a study of 500 males and 500 females with acute gonorrhea, Kemp and Shaw found that only 1 4 per cent of the former and 3.0 per cent of the latter had coexisting primary syphilis and that in every instance the chancre was clinically detectable These patients were all examined for the presence of genital lesions daily for the first three weeks after admission three times weekly for the following two weeks and weekly thereafter for ten weeks. On the other hand, Carley found 8 cases of early syphilis in patients with acute gonorrhea which he detected only by routine serologic follow up Unfortunately he fails to give data as to the total number of cases of gonorrhea from which these 8 were drawn and the frequency with which they were examined for the presence of genital lesions.

Recently Friedman has described a method for the demonstration of treponemes in gonorrheal pus. The results of this study are not applicable, however to the present discussion

Though the three explanations advanced may hold for many supposedly symptomless infections in man they fall far short of accounting for all. Recent experimental work affords a new and perhaps more logical approach to this question. It has been shown by Chesney Kolle, Brown and Pearce and Mahoney that in the usual experimental animal the rabbit, infection with syphilis may occur under certain conditions without the development of any initial lesions at the portal of entry or any subsequent generalized lesions. Other investigators have shown that such symptomless infections may be produced with regularity in the mouse and in certain other experimental animals. Morgan and his associates found that a minimal measured number of treponemes would not infect rabbits at all a slightly larger number would uniformly produce symptomless infection while a still larger number produced typical lesions at the portal of entry Although these experimental data are not directly applicable to man, they may nevertheless explain the absence of the usual manifestations of early syphilis in some patients. It is not illogical to believe that in man as in animals a variation in the size of the inoculum may materially influence the later course of the disease.

Just how frequently symptomless infection occurs is impossible to determine, but elsewhere we have hazarded the guess that at least one man of every five and one women of every three who acquires syphilis does so without ever developing any lesions recognizable as early syphilis.

The importance of symptomless infection from the treatment standpoint is twofold involving both the community and the individual. Such patients are a public health menace conceivably greater than patients with frank early lesions, since they may act as carriers of disease. Unrecognizable as syphilitic even to themselves they may unwittingly spread disaster to others. At present there seems to be no satisfactory method of approach to the public health question involved except an increasingly wide-spread routine use of serologic tests, with adequate sterilizing treatment for those found to be infected

From the individual standpoint such patients form an inexhaustible reservoir for the development of late syphilis. Unaware of their infection they are untreated and many of them ultimately develop serious or even fatal late lesions

The presence of virus in the blood in relation to treatment —With the spontaneous healing of lesions it is probable that treponemes disappear from the blood, to gain entry again, if at all only in small and irregular showers during the period in which relapsing infectious lesions are prone to occur After latency is firmly established, the presence of virus in the blood cannot be demonstrated by animal inoculation, and it is probable that except in one special circumstance organisms are actually absent. The special circumstance is pregnancy Unfortunately studies have not been made of the infectiousness of the blood in female patients with latent syphilis before during and after pregnancy, but since it seems unlikely that treponemes could reach the product of conception in any other way than via the maternal blood stream their presence in the mother's blood at some stage of pregnancy must be assumed

The development of immunity Refractoriness to reinoculation.—Almost as soon as infection has occurred there begins a slowly developing alteration in the reaction of the host's tissues to the invading organism. The first evidence of this is a change in the patient's behavior toward a second inoculation of organisms from without In experiments carried out both in animals and human beings, it has been shown that until about 15 days after the appearance of the chancre, a deliberate second inoculation will produce another chancre after the 15th day this is usually not possible The patient has become refractory to reinfection. This immunity is not absolute In animals it may be broken down by the use of heterologous strains or by varying the route of inoculation with homologous strains. If deliberate attempts at reinoculation are made in man a lesion may appear at the site of inoculation but it may not resemble a chancre, partaking in some instances rather of the characteristics of the particular stage of syphilis in which the patient happens to be at the moment. Once established, this state of resistance to reinfection persists during the lifetime of the animal or patient The development of it can be prevented by treatment given early in the infection, and successful reinfection with a homologous strain of virus in that case made possible (before the 45th day in rabbits Chesney and Kolle before during, or shortly after the secondary outbreak in man Halley and Wassermann) If treatment is delayed, however, until after the 90th day in the rabbit or until after the completion of the secondary period in man, these immune relationships are established and, so far as we know are not susceptible of disturbance by further treatment.

The relationship of resistance to reinoculation and the curability of syphilis.—The relationship between the susceptibility of animals or human beings to reinfection and the curability of syphilis is a fascinating problem. Neisser's experimental work led him to believe that ability to reinfect a treated experimental animal meant that the original infection had been cured resistance to reinoculation was dependent upon the persistence of foci of organisms in the body This concept which dominated the picture until the experimental studies of Chesney has been responsible for much of the pessimism of therapists. If it were true, the great infrequency of reinfection in man, even when treated early and its almost complete absence when treatment is begun late, would indicate that in human beings biologic cure, in the sense of eradication of the last remaining organism is rarely if ever possible Chesney and his associates have shown however that in experimental animals, treated either early or late in the course of the infection "cure," as measured by the rigid criterion of sterilization of tissues,* may be obtained, though reinfection is possible only in those treated early When treatment is started after the 90th day of the infection the animals, though apparently "cured usually remain refractory to reinoculation.

These experiments suggest that in rabbits, and presumably also by analogy in man, some degree of immunity against syphilis may persist after complete eradication of the infection. Together with the evidence

* This is demonstrated by lymph node or tissue transfer from treated to normal animals.

already mentioned that in untreated syphilitic animals the resistant state is not uniformly effective against heterologous virus they also suggest that reinfection is an unsatisfactory criterion of cure. It may occur in the face of persistent infection it may be impossible because of the persistence of the refractory state even though infection has been completely abolished.

This is a new concept of immunity in syphilis and one which is distinctly encouraging to the clinician If it is true then not only early but late syphilis also may be curable in the biologic sense As yet, however the experimental and clinical evidence cannot be entirely harmonized. In early syphilis both of animal and man experimenter and clinician agree that biologic cure is possible by means of maximum therapeutic attack. In late syphilis of man no one knows if sterilization of the tissues may be accomplished by treatment* certainly clinical serologic, and pathologic data all indicate that biologic cure if it occurs at all is relatively infrequent, and that a more attainable aim is clinical arrest If this be true, the intensity of therapeutic attack may be materially less in the late than in the early stages of the disease

Immunity in syphilis The interaction between host and parasite —It is necessary to reconcile the refractoriness of human beings to a second inoculation of virus from without, with the fact that such individuals develop lesions in skin and various other tissues as a response to their own virus coming from within. As Cheney states the generally accepted hypothetical explanation of this interesting phenomenon —"the treponemes develop a resistance against the treponemicidal agents of the host the former themselves become immunized as it were, and in this manner are able to resist a defensive mechanism which is fully capable of dealing with and destroying foreign virus. One may conceive of a balance struck between the host and the parasite a mutual immunization whereby the latter remains viable for decades in the body of the former without exerting any tissue reaction and perhaps without increasing in numbers yet is ever able and ready to initiate an inflammatory reaction should conditions (as yet imperfectly understood) favor the development of new generations of organisms and retains as a parasite the ability to infect and produce disease in a new host

"When for reasons as yet obscure the balance is disturbed and new inflammatory reactions are set up with the development of microscopic lesions do these new lesions represent an increase in the number of treponemes or an exaltation of their virulence, or both and is the reaction similar to that which would be exhibited by a normal individual or one in the early stages of the disease? Or is there evidence that the body of the syphilitic individual, by reason of the existence of syphilitic infection

* Because the lymph nodes of individuals with early syphilis are rapidly sterilized by treatment and may remain so even in the presence of inadequate treatment, and since it has been shown (Lake and Bryant, Lansford and Day Kemp, and McNamara) that the lymph nodes, semen and blood of individuals with untreated late syphilis are frequently non-infectious for rabbits, the method of tissue transfer is not available as a criterion of cure of syphilis in man.

within it for some time, has been changed and now reacts in an altogether different manner? All of the evidence is in favor of the latter view Clinical and pathological experience as is well known, shows that the tissues of the syphilitic individual, who has carried his infection for some time react toward his own virus in a manner altogether different from that of a normal person. The character of the late lesions is markedly different from that of the early ones—destructive and proliferative changes are in the ascendancy in the case of the former and yet it is the universal experience that treponemes are extremely scarce in tertiary lesions. The inflammatory response in late syphilis is indeed out of proportion apparently to the size of the stimulus, and this indication is sufficient to place the late tertiary lesions in the category of allergic phenomena. Moreover, animal inoculation has demonstrated that the organisms found in these lesions do not possess an exalted virulence, hence there is no reason to ascribe to changes in the virulence of the virus, the greater tissue response exhibited by the late lesion Rather on the other hand, should it be ascribed to changes in the host.

"It appears then, that that there develops in the syphilitic individual in the course of time a state characterized by an alteration in the way in which his tissues react to his own or a foreign virus. This alteration may take the form either of over-activity or of indifference toward the virus. The changed reaction capacity, as manifested by over-activity has been called by Neisser 'Umstimmung, and is synonymous with allergy To that altered reaction capacity which manifests itself as indifference to virus, he has given the term anergy It is his idea that the anergic and allergic states are not fixed states in the body of the individual but that they are continually undergoing alteration."

It is possible, as Chesney adds to explain the entire course of untreated syphilis on the basis of these states, affecting in turn the activity of the treponeme To the clinician it seems almost as if there were an 'allergic type of individual (about 25 per cent of all those infected) especially prone to develop gummatous late lesions in skin, mucosae, bones, or viscera, and relatively free from degenerative sequelae in cardiovascular or nervous systems. Others, also roughly a quarter of those infected, remain free from the explosive, allergic type of tissue reaction but respond to the presence of organisms with an exquisitely chronic, pathologically relatively insignificant but functionally important, inflammation and subsequent fibrosis in cardiovascular apparatus or nervous system. Still others, about equal in number, succeed in living in functional harmony with the parasite which produces tissue damage so slight as to cause no physiologic disturbance, even over the period of a lifetime these individuals maintain a state of prolonged latency and are recognizable as infected only by serologic tests. And finally certain patients, again roughly about 25 per cent of those infected, seem, so far as is determinable clinically, to attain a degree of resistance resulting in sterilization of the tissues and spontaneous "cure" These 'types" are of course not hard or fast there is considerable overlapping and many patients may for causes unknown change from one to another It would be of enormous benefit, from the

standpoints of prognosis and treatment if one could recognize, during the early months of infection, the probable type of response to be expected from a given individual. Perhaps studies in human constitution will provide a lead in this direction (Fleming)

Immunity in various body tissues The nervous system and the eye—Different body tissues appear to respond to infection in various degrees and to interact upon each other Thus an extensive, profuse secondary syphilis of the skin apparently protects the patient against late central nervous system involvement while on the contrary, most patients with clinical neurosyphilis have had relatively insignificant secondary lesions or none at all. Likewise, the individual who becomes hypersensitive—allergic—to his own organisms, and develops gummatous late lesions of skin, mucosae, or bones, is less likely to develop neurosyphilis while the converse is true of those in whom the lesions of late syphilis are characterized by microscopic fibrosis. Those clinical observations find some experimental confirmation in the work of Brown and Pearce who found that the extent and character of the initial response of rabbits to syphilitic infection determined to some degree the subsequent course of the disease Clinical observations also indicate (Keidel) that in some patients the body's own defense mechanism may deal successfully with invasion of the nervous sytem. It is assumed on what seem to be adequate grounds that the neuraxis is invaded by treponemes in every patient who acquires syphilis, at the time of the general dissemination of organisms. Only about 25 per cent of all untreated patients, however, develop clinical evidence of central nervous system involvement, as contrasted to the probable universality of invasion. In an additional 12-15 per cent, abnormalities are found in the spinal fluid though no clinical evidences of neurosyphilis exist. Of the remainder a considerable proportion (17 per cent) of patients with late syphilis but normal spinal fluids show suggestive neurologic abnormalities and it is probable that in them the body's own defense mechanism has cared for the situation.

By ingenious experiments Chesney and his associates have also shown that in the rabbit the eye does not share to the same extent as other tissues in the general resistant state which develops in that animal during the course of syphilitic infection and suggest that this phenomenon may be a partial explanation for the repeated relapses of interstitial keratitis in congenital syphilis

Active and passive immunization against syphilis—It is impossible to prevent syphilitic infection or to treat it successfully if once acquired by attempts to produce artificial immunity Limitations of space in this monograph forbid a detailed presentation of the evidence supporting this fact. It is summarized by Chesney as follows —"Attempts to produce in man or the lower animals active immunity to syphilitic infection by the utilization of derivatives of syphilitic tissue cultures of treponemes, syphilitic virus (living or dead) or products of the latter have been uniformly unsuccessful provided the disease itself was not produced Nor have such methods had much effect upon the course of an already established infection. Attempts to confer immunity to syphilis by

passive transfer of serum from immune persons or animals have likewise been fruitless. Apparently infection with virulent virus is necessary to produce immunity although perhaps not essential to maintain it

Treatment efforts by utilization of crossed immunity —The apparently close biologic relationship between the organisms of syphilis and yaws has naturally led to efforts to treat syphilitic patients by means of deliberate infection with yaws (Jahnel and Lange) The results of these efforts, carried out in paretics, have been negative or inconclusive and as a matter of fact much more experimental work is essential before further trial in man is justifiable For this same reason it seems advisable to withhold consideration of the attempts of Hilgermann Spitzer Neuber Kertesz, and others to treat patients with treponemal vaccines and immune substances derived from the organs of animals treated with such vaccines. Although some of these reports are promising, the total number of cases from which the results have been compiled is comparatively small. In addition, information concerning the effect of these substances in experimental animals is entirely inadequate

It has been suggested that at least part of the favorable effect of the treatment of general paresis with malaria might be due to crossed immunologic relationships between the plasmodium and the treponeme In order to gain the full advantage of the possibilities in this connection, other organisms more closely allied to the treponeme have been utilized in fever therapy namely the spirochetes of relapsing and of rat-bite fever Since the results with these infections are distinctly less good than with malaria, it is probable that the factor of crossed immunity plays a negligible if any part

The influence of antisyphilitic treatment on immunity —The treatment of syphilis by modern methods may under certain circumstances exert a disturbing influence on either or both of the elements of immunity which have been discussed, namely the response of the host to organisms freshly introduced from without and to his own parasites Man, like experimental animals may be rendered susceptible to reinfection by treatment. This may be accomplished only if treatment is begun early in the course of the disease in most instances before the sixth month. The time limits are not so sharply demarcated as in experimental animals, but certainly almost all the reported probable examples of reinfection have been in patients in whom treatment was started before the completion of the secondary period and the establishment of latency (Halley and Wasserman) After this period, no amount of treatment will alter the refractory state Even in patients treated early reinfection does not necessarily imply the complete cure of the first infection theoretically, at least superinfection is possible and there are no adequate methods to differentiate between the two

Treatment may also interrupt or depress the process of formation of the patient's gradually developing immunity to a point at which, while still resistant to organisms freshly introduced from without, he is left without adequate defense against the treponemes in his own tissues. Under these circumstances if the treponemicidal influence of treatment is withdrawn

short of the point of complete sterilization of the patient, a fresh multiplication of organisms in tissue foci a fresh dissemination through the lymphatics and blood stream and fresh implantation in tissues which have previously escaped or have been sterilized, may occur This may be manifested by the phenomena included under the general heading of early infectious relapse—delayed or recurrent cutaneous or mucosal secondary lesions, ocular relapse neurorecurrence.

This interference by treatment with the patient's resistance to his own organisms is limited though within wide time limits, to early syphilis, as is the factor of resistance to reinfection. In the latter case the average upper time limit is probably well within the first year after infection in the former it may extend to as long as four years. After this period of time has passed, it is probably no longer possible for treatment to alter the patient's defense mechanism against organisms either from within or without. Treatment less than sterilizing in amount does not favor relapse It may fail to prevent progression in lesions already present, but it does not cause an increased incidence of fresh lesions in apparently uninvolved tissues. Apparently therefore in man resistance may be for a time more effective against organisms from without than against those already present in the patient's tissues.

This conception of immunity is of fundamental importance in planning treatment for syphilis. If treatment stopped short of the point of complete sterilization of the patient is likely to interfere with developing immunity but not to disturb it once firmly established it follows that in early syphilis treatment must be *continuously* carried out until the point of complete sterilization is reached that therapy must wholly or in large part replace the patient's own defenses In late syphilis this is less essential. Reference to this point will echo throughout this whole book.

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Chapter III

THE PROGNOSIS OF UNTREATED AND TREATED SYPHILIS AS TO INFECTIOUSNESS AND CURE

When once the diagnosis of syphilis has been established and the patient has recovered from the shock of hearing it, his first questions will deal with his potential infectiousness for others, the possibility of cure of his own disease and the likelihood of ultimate disaster These questions cannot be intelligently answered, nor indeed the patient intelligently treated, unless both physician and patient have clearly in mind first, as to what is meant by the use of the words "infectiousness" and "cure" and second, what will be the probable developments under the three circumstances of no treatment, poor treatment, and good treatment.

The Infectiousness of Syphilis

How do infections occur? The immediate death of the treponeme on drying limits the transmission of syphilis from adult to adult. The organism can pass from an infected to an uninfected person only by means of direct or close indirect contact of moist surfaces of the body These moist surfaces are two the genital and the buccal mucous membranes In the vast majority of cases (about 95 per cent) therefore, infection is transmitted through sexual intercourse. The remaining 5 per cent of infections are extragenital, most of which develop as a result of some practice primarily sexual e.g., about the mouth (at least half of all extragenital chancres occur here) usually from kissing on the nipples (also from kissing or biting) at the anus or elsewhere near the genitalia (from sexual perversion) Infection from non-sexual sources is commonest as the "professional chancre" on the hands of physicians, dentists nurses and midwives.

There is little risk of purely accidental infection from household contact, the common drinking cup eating utensils, clothing, linens barber shops and beauty parlors. Such infections do occur but are insignificant in comparison with sex infections. Not more than 50 examples of syphilis of non-sexual accidental acquisition can be identified among more than 35 000 syphilitic patients in the Johns Hopkins material—a risk approximating 0 01 per cent.

While the patient should be warned against the possibility of infecting others by casual means, it is safe to assure him and his intimates that the greatest danger lies in the common sexual contacts of intercourse or kissing.

Is the infectious agent always visible and spirochetal?—It has been contended by some workers, notably Levaditi and Nyka, that *T pallidum* may undergo cyclic changes from a spiral to a granular even to an infra-visible form and that the latter often, perhaps always, may be the infecting form. The opposite point of view has been as stoutly up-

held by others, especially Bessemans At present, the most that can be said is that the evidence for the existence of any other form of the treponeme than the well known spiral is unconvincing, and that Bessemans and his group appear to have the better of the argument.

What lesions of syphilis are infectious?—In broad general terms it may be said that the mucosal lesions of early syphilis whether congenital or acquired, are infectious These, the chancre and the mucosal lesions of early secondary or relapsing secondary syphilis contain large numbers of readily demonstrable treponemes. Stress is laid on mucosal rather than cutaneous lesions since the former are moist, the latter usually dry Moisture, it will be recalled is a prerequisite for transmission of infection. The infectious mucosal lesions may range in size from the huge condylomatous genital masses so often seen in Negroes to a macroscopically invisible break in continuity of buccal or genital mucous membrane. It may be safely assumed that any patient with early cutaneous lesions is potentially dangerous to others whether or not *visible* mucosal lesions can be demonstrated.

It is important to recall that infectious mucosal lesions occur as part of the original outbreak of early syphilis to persist until complete healing occurs whether spontaneous or under the influence of treatment and also that in many untreated patients if not in all, they continue to appear in crops for months or even years usually distinguished by lesions decreasing in number and increasingly trivial. Finally even though the patient is untreated, immunity develops and actual mucosal lesions cease to appear

In equally broad general terms, it may be said that late lesions of syphilis are not infectious. Even though they are moist and on the surface of the body (the broken down gumma) they contain few if any organisms.

Does exposure to a person with infectious lesions always result in infection?—The material of the C.C G indicates that even repeated sexual exposure to a person with infectious mucosal lesions does not always result in infection as usually believed which instead occurs in about 90 per cent of such exposures The Group has observed at least 50 families in which husband or wife has escaped infection in spite of repeated intercourse with a partner who had darkfield positive genital lesions at the time The factors which account for this protection are not clear They probably depend less on natural immunity which is probably non-existent, than on personal cleanliness. There is probably less danger for the man especially if circumcised, who washes thoroughly with soap and water immediately after intercourse or the woman who in addition to a thorough vulvar washing, also uses an immediate cleansing douche than for those who postpone or omit this detail of personal hygiene

It is further probable, though not yet proved that the increasing use of contraceptive jellies may afford some protection against the transmission of syphilis, and of gonorrhea as well. These jellies are usually strongly acid, with a pH in which the treponeme cannot survive

When is syphilis infectious?—It is a common clinical impression

that infectiousness is closely related to the duration of infection. There is some risk of infection of a sexual partner even during the incubation period of the disease In the material of the C C G there were 33 persons who had sexually exposed their marital partners from 1 to 14 days *before* the first appearance of lesions of syphilis infection of the partner resulted in 4 cases an incidence of 12.1 per cent.

It is assumed that after lesions have developed, the danger of direct transmission to others is greatest within the first year is still great during the second year and is rapidly less so as further time goes by By the end of the fifth year the risk is slight whether patient is male or female treated or untreated.

The difficulty of demonstrating the truth of this assumption is nearly insuperable. The C.C G has attempted a statistical study of the incidence of syphilitic infection among the marital partners of persons infected with syphilis before marriage and at varying intervals after it. Because of unavoidable selection of material (failure to attain random sampling), the fallibility of human memory for past trivial events, the difficulty of positive identification of the spouse as the source of infection, rather than some premarital or extramarital contact and various other uncertainties, the results were essentially meaningless An exact definition of the duration of infectiousness of syphilis, treated or untreated, seems impossible to attain. The statement that infectiousness is almost always limited to the first five years probably must rest on clinical impression. In this same C C G study however there was determined the syphilitic status of one member of a family (husband or wife) *when the other had demonstrable early syphilis* Four hundred and sixty families were available in each of which one partner had early syphilis. The other partner was observed to have early syphilis in 67 1 per cent of the families an additional 31 per cent had latent syphilis of less than 2 years duration and in only 1 7 per cent could the recent infection of one partner be tentatively attributed to late syphilis (of more than 2 years' duration) in the other From this approach, it may properly be concluded that a patient with early syphilis usually acquires his infection from another who also has early syphilis at the time of exposure and almost always from one who has been infected within 2 years before exposure.

Our own practical experience confirms these observations. After the fifth year the risk of infection from a syphilitic partner male or female, previously treated or untreated, even by the intimate contact of sexual intercourse is certainly 1 in 20 or less after the tenth year 1 in 100 or less.

These data do not apply to the risk of infection of a child in utero by its mother The danger to the fetus is directly related to the duration of infection in the mother and is greatest in the first year but is not entirely obviated by the mere passage of time.

It is not possible however entirely to ignore the risk of infection of a sexual partner from a person with late syphilis All such partners must be thoroughly examined. Furthermore the risk of infection of a fetus cannot be ignored so long as the infected mother remains within the child-bearing age

Is syphilis infectious in the absence of lesions?—The probability that infectiousness largely disappears after the fifth year fits well with the known facts as to occurrence of early or relapsing mucosal lesions. Is it possible however that infection may be transmitted in the absence of such lesions? To this question no categorical answer can be given. It is known from experimental studies, though obviously not in human beings, that the treponeme can penetrate the unbroken mucous membrane of a normal animal e.g. the preputial or conjunctival sac In recently infected

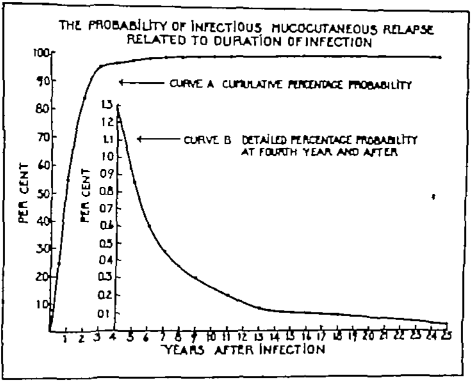


Fig. 1

persons, treponemes can be found in normal skin or mucous membrane in which no lesions can be demonstrated. In the very nature of the case, we are unlikely to discover either in experimental animals or human beings whether organisms can penetrate such an intact mucosa from within outwards. The C C G evidence that 31 per cent of a series of 460 patients with early syphilis had apparently acquired their infections from persons with latent syphilis does not provide an answer to this question. The donors of the infection in these cases had no visible lesions at the time of examination but may well have had them at the time of the infecting exposure

The relationship of infectiousness to infectious relapse—There is no information available as to the incidence of infectious mucosal relapse in untreated syphilis because no observer ever has followed or

will be able to follow a large series of untreated patients with *frequent* recheck examinations Since 1493 most patients with early syphilis, if recognized, have received some form of treatment. Those who were not treated were unrecognized if recognized, were not followed.

Disregarding the factor of the kind and amount of treatment given, however Fig 1 shows the time relationships of infectious mucocutaneous relapse, based on our own experience and the monumental data of Fournier and of the C.C G Curve A represents the cumulative percentage likelihood of appearance of infectious relapse lesions as related to duration of infection It shows that approximately 25 per cent of all relapses may be expected in the first six months 55 per cent within the first year 84 per cent by the end of the second and 95 per cent by the end of the third year of infection About 5 per cent of all such relapses occur during the fourth year or later and curve B on a much more detailed scale shows in fractions of 1 per cent the probable expected incidence as time goes on. Infectious relapse has been observed though rarely as late as the twenty fifth year

While it seems unnecessary to assume that a patient may transmit infection through his own intact mucosa, there is still a possibility that an infected female, herself non-infectious because of the duration of her own disease or for other reasons, *may act as a passive carrier of treponemes.* For example, the vagina of an infected though non-infectious prostitute might conceivably contain treponemes deposited there by one partner through which she infects the next. This again is only speculation since numerous efforts to demonstrate treponemes in the vaginal or cervical secretions of women with late syphilis and no lesions have been fruitless (Pariser)

TABLE I

INCIDENCE OF INFECTIOUS RELAPSE AS RELATED TO STAGE OF DISEASE AT THE START OF TREATMENT

(Data of the C.C.G)

Stage of disease	Total cases observed	Percentage of patients developing infectious relapse
Seronegative primary	342	10 4
Seropositive primary	885	20 2
Early secondary	2252	9 6

Infectious relapse and stage of syphilis.—As is shown by the data of the C C G (Table 1) infectious relapse is paradoxically more frequent in primary than in secondary syphilis under identical conditions of treatment This is surely due to the fact that by the time the patient has developed the generalized tissue reaction of secondary syphilis his own resistance against the infection is enhanced. The data are convincing evidence that in this respect, at least primary syphilis should be treated as energetically and for as long a time as secondary syphilis.

Antisyphilitic treatment and infectiousness —Of the several available antisyphilitic drugs, the trivalent arsenicals alone (the arsphenamines and mapharsen) are *of value in controlling infectiousness rapidly* and nearly completely Mercury probably has no effect at all patients treated with it relapse in about as high a proportion as if no treatment had been given. Bismuth controls infectiousness slowly days or weeks are *required for the disappearance of surface organisms from lesions Nothing*

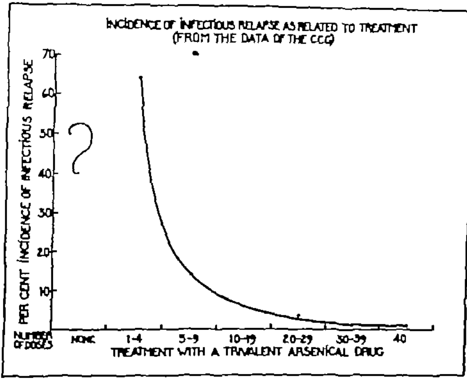


FIG. 2

definite is known as to the incidence of relapse in patients treated with bismuth only since few have been so treated.

The effect of a single injection of a trivalent arsenical —When an *adequate* dose of an arsphenamine or of arsenoxide is given to a patient with infectious lesions treponemes demonstrable by darkfield disappear within 2–6 hours Thereafter the patient is non-infectious for all practical purposes and except by the most intimate contact The rapidity of disappearance of surface organisms or indeed whether they disappear at all, is directly proportional to the size of the dose (cf p 80) For example while a dose of 0 060 gm. of mapharsen will destroy surface organisms in 6 hours a dose of 0 040 gm may require 24 hours and one of 0 020 gm. may fail completely

The duration of non infectiousness after a single dose of an arsenical

drug is not definitely known but is probably at least 2–3 months the shortest interval at which relapsing lesions usually occur

The effect of multiple doses of trivalent arsenicals —The data of the C.C G relate almost entirely to arsphenamine (606) but probably hold good for other arsphenamines and for mapharsen (arsenoxide) They are presented graphically in Fig. 2. Since the incidence of infectious mucocutaneous relapse in untreated patients is unknown, no comparison can be made as between treated and untreated groups. Among treated patients the incidence of infectious relapse shown in Fig 2 is a minimum for it represents only patients actually observed because of the triviality of relapsing lesions many (perhaps most) such patients are not observed at the time Of those who receive only 1–4 injections of an arsenical drug, however nearly 65 per cent later develop infectious relapse When 5–9 injections are given, the proportion drops to about 12.5 per cent with as *many as 30 injections (now of course with concomitant heavy metal)* to about 1.2 per cent.

Although it appears from Fig. 2 that infectious relapse is inevitable in about 1 per cent of patients no matter how much treatment is given, this datum does not take into account the system of treatment. As is suggested by Table 2 and as will later appear (Chapter XIII) when 30 or

TABLE 2

INFECTIOUS RELAPSE AS RELATED TO TREATMENT SYSTEM (DISREGARDING AMOUNT GIVEN) AND SEROLOGIC OUTCOME

(Data of C.C.G)

Treatment System	Percentage of patients with early syphilis developing infectious relapse when serologic result under indicated treatment scheme was	
	"Normal reversal	"Delayed reversal
Continuous	2 5	6 7
Intermittent	8 2	15 9
Irregular	12 8	42 2
Intensive	4 3	14 3

more injections of an arsenical with concomitant heavy metal are given to a patient with early syphilis by the *continuous* system the incidence of infectious relapse approaches the vanishing point.

Chronic relapsing and treatment resistant syphilis —About 1 in 200 patients with early syphilis exhibits the closely related phenomena either of chronically repeated infectious mucocutaneous relapse or of treatment-resistance In the former case, the cessation of treatment

The incidence of infectious relapse in patients treated with the 5-day intravenous drip massive dose technique cannot yet be accurately estimated, but with mapharsen is probably about 12 per cent (cf Chapter XXXIII)

whether planned or fortuitous is followed shortly by relapse in the latter infectious lesions fail to heal and remain darkfield positive in spite of continuing treatment. The mechanism of these complications thoroughly discussed by Beerman probably lies not in the failure of drugs but rather in the failure of the patient *to develop the usual degree of resistance* (immunity) against his own organisms.

While such patients unquestionably are a potential source of community danger they are so infrequent as to be much less dangerous than the more usual patient who develops trivial and inconspicuous relapsing lesions The management of this situation presents a special problem discussed on p 222

The blood test and infectiousness—There is absolutely no relation between the result of the blood test and actual or potential infectiousness This statement is so important as to receive especial prominence as Fig 3 Primary syphilis is of course infectious during the few days before the blood serologic test becomes positive In patients with infectious

FIG. 3

THE BLOOD TEST AND INFECTIOUSNESS
ARE *NOT* RELATED!

1 Many patients with *negative* blood serologic tests *may be infectious* e.g., in seronegative primary syphilis, during infectious mucocutaneous relapse.
2. Most patients with *positive* blood serologic tests *are not infectious* e.g the vast majority of all patients with late and latent syphilis of more than 5 years duration.

mucocutaneous relapse seropositivity is by no means so universal as during the original outbreak of secondary syphilis and depending on the sensitivity of the serologic test employed the incidence of positive reactions during the period of infectious relapse ranges only from 50–90 per cent

In untreated late syphilis of whatever type (and of more than 5 years *duration*) the blood serologic test is usually positive (95 plus per cent) but such patients are not infectious

Ignorance of this point has led physicians social hygienists, and legislators into errors tragic both to individual and the mass

Instructions to the patient regarding infectiousness—The preceding considerations permit some definition of practical instructions from physician to patient regarding infectiousness These are summarized in Fig 4 The advice regarding sexual intercourse is a compromise of the desirable with the practical It is obvious that if the marital (sexual) partner is uninfected, the patient with early syphilis should avoid intercourse while open lesions are present As soon as they have healed he may

FIG. 4

INSTRUCTIONS TO THE PATIENT FOR THE PROTECTION OF OTHERS

A. If the patient has early syphilis (less than 5 years duration)

1. Avoid sexual intercourse completely for 6 months.
2. If treatment has been continuous for 6 months, intercourse may be resumed if treatment continues and *during the arsenical phase of therapy only* and with mechanical (condom) protection only. It is further desirable to use a small amount of 33 per cent calomel ointment as a lubricant.
3. Unprotected sexual intercourse should not be permitted until completion of treatment and subsequent symptomless year of probation.
4. Avoid moist kissing of sexual partner or others, especially children, until completion of treatment and probation.
5. Sleep alone.
6. Do not let another person put in his mouth moist objects which have been used by the patient (eating utensils, pipes, cigarette holders, etc.).
7. Household contact is not dangerous after treatment is started, though any form of sexual contact may be.
8. The first injection of an arsphenamine destroys surface organisms promptly (24 hours): start it at once.
9. To prevent infectious relapse, *treatment must be continuous for a minimum of 40 weeks, better 60 weeks. No lapses or rest periods.*

B. If the patient has late syphilis (more than 5 years duration)

1. If marital or sexual partner is already infected, no precautions of any kind are necessary.
2. If marital or sexual partner is uninfected:
   a) Avoid unprotected sexual intercourse and moist kissing until after 6 months' treatment. During this period mechanical (condom) protection. Thereafter no precautions necessary.
   b) Household or casual contact infection is not to be feared.

C. *For the prevention of congenital syphilis*

1. Treat the infected mother throughout every pregnancy regardless of the type or duration of her own infection or of the amount of preceding treatment. *Start treatment as early as possible in pregnancy.*

be non-infectious at once and may remain so provided that (a) treatment is continued and continuous to the point necessary to eliminate the possibility of infectious relapse and (b) he is neither a "chronic relapser" nor treatment-resistant. To guard against these two possibilities, abstention from intercourse for six months should be insisted upon. This period is long enough to demonstrate the patient's willingness to undergo continuous treatment and to eliminate at least the treatment-resistant group. It is not so long as to cause the average patient to disregard the advice. After six months and provided treatment continues intercourse with

mechanical (condom) protection may be permitted, but since relapses tend to occur during the heavy metal phase of therapy this should be limited to the period when an arsenical is being given. The restriction on unprotected intercourse until completion of a probationary year after treatment is an obvious protection not only against infection of the partner but also against pregnancy

As to kissing it is essential to emphasize to the patient that the friendly kiss (on the cheek, for example) with dry lips is harmless whereas the moist kiss, whether from simple wetting of the lips or with the tongue, may be dangerous

If the infected person has late syphilis and the marital (sexual) partner is uninfected unprotected intercourse is probably safe from the start the mechanical (condom) protection does no harm and is often an aid in facing the psychologic hazards involved.

Are body secretions infectious?—Animal experimentation has shown that various body secretions e.g. saliva, urine, tears milk, semen are under certain conditions infectious The only two of these of practical importance are semen and milk. Because of the apparent infectiousness of certain male patients with recent infections but no obvious lesions or even with long-standing infections it has been clinically assumed that seminal infection might occur frequently The recent work of Kemp shows, however that while semen may often be infectious when the male has obvious lesions of early syphilis (in which case organisms may possibly enter the semen by virtue of its passage over open mucosal lesions in the lower urinary tract) it is rarely so if ever when the male has had syphilis more than 4 years whether previously treated or not. Though seminal infection may infrequently occur it can hardly be a common method of transmission of the disease.

Milk may account for the infection of some few nursing infants for which reason a healthy baby born of a mother recently infected with syphilis (i.e. within 4–5 years) should for complete safety be fed on the bottle from birth.

The infectiousness of blood—Transfusion syphilis.—Many more instances of transfusion syphilis occur than are reported Emphasis has been laid on this topic through recent papers by Klauder Morgan Rein, and others It is clear that the blood of any recently infected person is dangerous It is impossible to set any definite time limit on the infectiousness of blood since cases of transfusion syphilis have been reported from donors infected at least 7 years but the same general rule holds as for other methods of transmission i.e the longer the duration of syphilis in the donor the less chance of infection of the recipient This is clearly shown by the experience of McNamara, who in grave emergency used the blood of donors with outspoken late syphilis without the development of disease in the recipients

The best practical method of avoidance of transfusion syphilis is the rejection of all infected donors. Certain suggestions for the examination of donors are shown in Fig 5

Utilizing the principle of the treponemicidal activity of the arsenicals

RULES FOR THE SELECTION OF DONORS FOR TRANSFUSION

1. Inquire for a history of syphilis.
2. Examine the donor physically for evidences of recent infection (to rule out seronegative primary syphilis).
3. Do a sensitive serologic test (if possible Kline exclusion or Kahn presumptive) on the donor before each transfusion.
4. Examine relatives and friends as carefully as professional donors.
5. Discard all donors with history, physical or serologic evidence of syphilis except in case of life saving emergency.
6. If a syphilitic donor must be used, add an arsphenamine to the citrated blood (see text).

in vitro discovered by Eagle, Kolmer and his associates have recently shown that blood seeded with treponemes may be made safe for transfusion by the addition of small quantities of an arsphenamine. If the use of blood from a syphilitic donor is absolutely necessary, therefore, the recipient may be protected against infection by adding to blood for a transfusion of average size 0.3 gm. of neoarsphenamine dissolved in 10 cc. of salt solution.

The risk of transfusion syphilis may be still further minimized by the recent widespread adoption of "blood banks" or of dried (lyophile) plasma as a source of donor's blood. Under experimental conditions (Turner and Diseker and Bloch*) treponemes apparently do not survive in blood stored at icebox temperature for longer than 72 hours, and are quickly destroyed by drying in the lyophile apparatus (Turner, Bauer and Kluth, Kemp*). The danger of infection of a recipient by the inadvertent use of a seronegative syphilitic donor is therefore probably eliminated if only dried plasma, or blood stored for 5 days or longer, is used for transfusion.

The "Cure" of Syphilis

The wide publicity recently given to syphilis in the lay press has aroused grave fears in the minds of patients as to the curability of the disease. Quoting from scientific publications, articles intended for laymen remark, for example, that 85 per cent of cases (of early syphilis) may be "cured"† if treatment is immediate and adequate, that this probability drops to 65 per cent if treatment is delayed a few weeks, and to 58 per cent if it is still further delayed, and that late syphilis is not generally "curable," though in many instances symptoms may be ameliorated.

* Unpublished data.

† Throughout this monograph, for reasons which appear in the text discussion, the word "cure" always appears in quotation marks except in the case of biologic cure where, for obvious reasons, the quotation marks are superfluous.

mechanical (condom) protection may be permitted, but since relapses tend to occur during the heavy metal phase of therapy this should be limited to the period when an arsenical is being given The restriction on unprotected intercourse until completion of a probationary year after treatment is an obvious protection not only against infection of the partner but also against pregnancy

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Utilizing the principle of the treponemicidal activity of the arsenicals

recorded deaths from syphilis (infantile or in adults specified as general paresis, tabes dorsalis, and aneurysm), there can be little hesitation in agreeing that syphilis ranks with cancer tuberculosis, and pneumonia as one of the four greatest killing diseases.

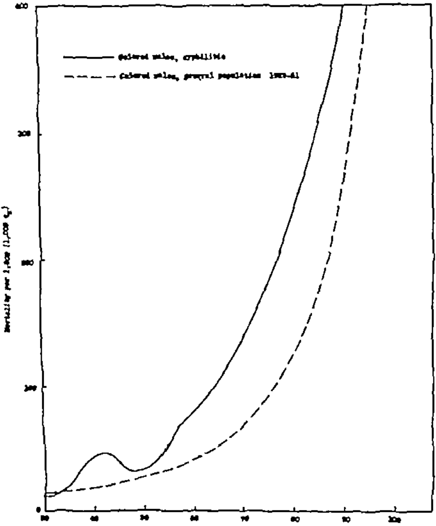


FIG. 7 —Rate of mortality per 1 000 (1,000 q_x) in Negroes with acquired syphilis and in general population (Dalton and Miner) Figures on base line represent age at death.

Prognosis from the actuarial standpoint —From the actuarial standpoint it is generally agreed that syphilis imposes an added risk of death as compared with non-syphilitic individuals in the proportion of 133 to 100 Reckzeh estimates that one of every three syphilitics dies as a direct or indirect result of this disease *In a careful study of material of the*

C G G Usilton and Minor found that syphilis shortened the life expectancy of white males between the age of 30 and 60 years by 17 per cent, and of Negro males between the same ages by 30 per cent

An extensive investigation the results of which were furnished us by Dublin covers life insurance issued from 1909–1927 It includes a large series of patients, probably a significant number of whom were treated by modern methods, including the arsphenamines This experience is summarized in Table 4. It is a striking fact that the ratio of actual to expected deaths is significantly higher in patients presumably cured than in those known not to be cured. The explanation for this phenomenon is not apparent but may lie in the possibility that less care is exerted by insurance examiners when the applicant s private physician states that the syphilitic infection is cured" than when no such information is available Another possible explanation is offered by Hall who utilized actuarial data to study the cause of death in 43 756 persons who had received at least two years of 'modern treatment for syphilis and who had been symptom-free and seronegative for at least one year before they were issued life insurance He found that the mortality among this group of persons was 147 per cent of the expected mortality in a similar group of non-syphilitic individuals Pulmonary tuberculosis, pneumonia and cancer were from one and three-fourths to two and one-half times more frequent as causes of death than among non-syphilitics These findings suggest that the patient who contracts syphilis is faced with a triple hazard an unfavorable outcome of his infection, the possibility of fatal reaction to treatment, and lowered resistance to other diseases A final evaluation of Hall s findings, however depends upon a more thorough statistical study of his material as well as confirmation from other sources

TABLE 4

ACTUARIAL DATA SHOWING ACTUAL AS COMPARED WITH EXPECTED MORTALITY IN A GROUP OF SYPHILITIC PATIENTS INSURED BETWEEN 1909–1927

(From the Actuarial Society of America and the Association of Life Insurance Medical Directors of the United States and Canada)

	Type of syphilis	Accepted by insurance companies as	Individuals	*Ratio of actual to each* 100 expected deaths
Not cured	(a) No details, (b) thoroughly treated not cured, (c) inadequately treated not cured (d) inadequately treated cured	Standard risk	7 269	142% ± 11
		Substandard risk	23 974	141% ± 7
Cured	Cured, thorough treatment	Standard risk	6 401	163% ± 13
		Substandard risk	20 247	150% ± 8

The pathologist's attitude toward prognosis —The pathology of syphilis has been studied by many observers, chief among whom is Warthin who made the subject the major effort of his life's work. In a number of important contributions, he has pointed out the great frequency of microscopic lesions which he attributes to syphilis, in patients in whom the disease was clinically quiescent or apparently cured. In 1 675 necropsies on patients over 25 years of age performed on his service between the years 1909–1923 he found what he calls lesions of latent syphilis in 501 or 29 per cent To illustrate the inefficacy of modern treatment methods, he says that he has "never seen at necropsy a case of perfectly healed syphilis," though how anyone could recognize the presumably non-existent lesions of "perfectly healed syphilis" is not apparent. His various publications convey the impression that in his patients, syphilis must often have been the cause of death, and tend, in our opinion, to over-emphasize its importance as a killing disease. Though the major burden of Warthin's argument was to illustrate the great prevalence of syphilis in the general population rather than to emphasize its importance as a cause of death it is unfortunate that he the most assiduous student of the pathology of the disease, did not furnish details as to four important facts (1) the cause of death, (2) whether the syphilitic infection was recognized during life (3) the degree and extent of pathologic damage to serve as an index of functional incapacity and (4) exactly what treatment had been given to those patients whom he classifies as clinically "cured" but pathologically still active

That the presence of microscopic lesions according with Warthin's criteria does not necessarily imply sufficient anatomic damage to produce physiologic or functional disability is indicated by the fact that another competent pathologist, Symmers, working at Bellevue Hospital, could find gross (not microscopic) lesions of syphilis in only 6.5 per cent of 4,880 autopsies. Not even in all of these patients were the lesions of syphilis visible to the naked eye, responsible for the patient's death.

In the Johns Hopkins Hospital, a study of 105 cases of uncomplicated syphilitic aortitis (without regurgitation or aneurysm) grossly recognizable at necropsy (Moore, Danglade, and Reisinger) showed that syphilis was directly responsible for death in only 20 per cent the lesion being a purely incidental finding in the remainder

Further pathologic studies in patients treated for syphilis are urgently needed which will correlate the findings with the character and amount of treatment given during life. The tedious time-consuming and expensive nature of this type of study has prevented confirmation of many of Warthin's revolutionary conclusions

Prognosis from the serologic standpoint —The physician who views his patients from the purely serologic standpoint will find himself in serious difficulties when he attempts to offer prognostic estimates. Persistent clinical and pathologic activity and progression of the disease may occur in the face of persistently negative serologic tests of blood and spinal fluid. On the other hand, many patients, treated or untreated, go peacefully through life with no evidence of infection except a positive serologic

test of the blood. In many patients with late syphilis, as will appear in *later sections of this book*, no amount of antisyphilitic treatment will be successful in reversing a positive serologic test to negative, the patients are seroresistant (Wassermann-fast) How interpret this phenomenon? Does it always mean that foci of organisms and active lesions persist somewhere in the body? Or is it possible that the blood serologic test may remain positive after all lesions are healed and the last treponeme dead an expression of immunity remaining after the infection has been eradicated as a positive Widal test may persist after typhoid fever? This would accord with Chesney's hypothesis of the possibility of biologic cure and its relation to persistent immunity in late treated syphilis in the rabbit. The answers to these questions are not yet clear though a faint light is beginning to shine. The serologist would say if he relied entirely on the laboratory that adequately treated early syphilis was nearly always curable, late syphilis rarely so

The clinician s concept of prognosis —What does clinical experience offer? The great student of the last century Fournier without the knowledge of the organism supplied by Schaudinn of serologic tests provided by Wassermann and his co-workers or of chemotherapy furnished by Ehrlich, thought that every patient who acquired syphilis and was not treated for it, sooner or later developed late (tertiary) lesions of one sort or another The serologic test, in addition to supplying information as to the widespread distribution of syphilis in the population upset Fournier's conception for it became evident that many patients with a positive test for syphilis went through life with no other clinical evidence of infection and died at a ripe old age of some other disease.

There is general agreement among clinicians that syphilis is curable early syphilis in the biologic sense late syphilis in the symptomatic sense. These conclusions are based on the one valuable criterion of prolonged observation of the patient over a period of many years.

Lesser was one of the first to suggest that spontaneous cure in syphilis not only did occur but that it was the natural tendency of the disease. To determine the accuracy of this conception is extremely difficult. To students of the disease it is becoming increasingly apparent, as Stokes and DesBrisay pointed out some years ago that even in untreated patients there is a *tendency toward* spontaneous reversal of positive serologic tests of blood and spinal fluid alike. The longer the duration of the infection, the more likely is such spontaneous reversal to occur The same phenomenon may be observed after the cessation of treatment in apparently seroresistant treated patients with late syphilis (cf pp 268, 279 and 454)

The spontaneous cure of syphilis —As we have pointed out, spontaneous serologic reversal is not necessarily synonymous with "cure." The only way to solve the problem of spontaneous cure would be to study and to determine the ultimate outcome, clinical and serologic, of a large group of untreated patients with early syphilis after a period of many years. Fortunately a series of such cases exists and has been reported by Bruusgaard. The chief of the Syphilis Clinic in Oslo between the years

1891–1910 Boeck, believed that little or nothing was accomplished by the mercury or potassium iodide treatment of syphilis, and that the ultimate result was equally good if one relied almost entirely on the patient's own defense mechanism. Accordingly, all patients with primary or secondary syphilis were given no treatment at all, or only a little mercury or potassium iodide by mouth. Within this time period 1891–1910 there were 2,181 such patients. During the later years, 1925–1927, Bruusgaard set out to follow these individuals. He succeeded in re-examining 309 of the original number at intervals ranging from 3 to 40 years after infection. In addition, he was able to determine the cause of death in 164 others, in 40 of whom necropsies were obtained. For various statistical reasons pointed out by Sowder in a re-analysis of Bruusgaard's study, these 473 patients probably do not constitute a random sample of the entire group. There is statistical reason to believe that if the whole group of 2,181 patients could have been studied, or if random sampling could have been attained, the results would have been even more favorable than Bruusgaard reports.

All the living patients were submitted to thorough physical examination with special emphasis on cardiovascular and central nervous systems. All had blood serologic tests, though spinal fluid examination was rarely employed. The results of this survey are presented in Table 5 and summar

TABLE 5

THE OUTCOME IN UNTREATED EARLY SYPHILIS (MODIFIED FROM BRUUSGAARD)

Of 2,181 patients with primary or secondary syphilis admitted to the Oslo Clinic 1891–1910, who received either no treatment, or only a little mercury or potassium iodide by mouth, author followed (1925–1927) 473, of whom 309 were living, and 164 dead.

Part I:	309 living patients*			
Status of patient at time of final examination	Interval between infection and final examination			
	30–40 years	20–30 years	10–20 years	3–10 years
Neurosyphilis	8†	10	11	4
Cardiovascular syphilis	9†	10	1	—
Skin, mucosal, or bone syphilis	2	8	21	27
Symptom-free, seropositive	11	18	9	29
Symptom-free, seronegative	35	54	24	19
Total cases	64	100	66	79

* All cases had thorough physical examinations, with especial emphasis on heart and nervous system. Spinal puncture rarely employed. Later developments may therefore reduce the groups of symptom-free seropositive and seronegative patients.

† One duplication.

Part II	164 dead patients (necropsy in 40)					
Cause of death		Duration of infection				
		3–10 years	10–20 years	20–30 years	30–40 years	Total
Syphilis certain 19	Cardiovascular syphilis	—	3	8	3	14
	Neurosyphilis	—	—	3	2	5
Syphilis questionable 38	Probably cardiovascular syphilis	1	10	10	6	27
	Probably neurosyphilis	—	1	4	2	7
	Other forms of syphilis, probable or certain	1	—	3	—	4
Other causes 107	Cancer tumor	2	7	10	10	29
	Tuberculosis	4	17	7	1	29
	Other diseases	5	20	18	6	49

ized in Table 6 which will amply repay detailed study When left to evolve spontaneously neurosyphilis occurred in 9.5 per cent of patients cardiovascular syphilis in 12.8 per cent, and the incidence of each increased with the passage of time In all a total of 23 1 per cent of these patients developed a serious often fatal, late lesion of syphilis In an additional 12.2 per cent some late lesion of skin mucosae, or bones developed disfiguring perhaps but not fatal However if one includes the patients who died from some disease not related to syphilis no less than 64.6 per cent of the total number of patients passed through the whole period of observation without being seriously inconvenienced by their disease and in 27 9 per cent spontaneous cure was the apparent result.

TABLE 6

SUMMARY OF BRUUSGAARD'S DATA AS TO ULTIMATE OUTCOME OF UNTREATED EARLY SYPHILIS

Patients showing at re-examination or death	Per cent of total number (473 patients)
Neurosyphilis	9 5
Cardiovascular syphilis	12 8
Benign late syphilis	12 2
Latent syphilis (no clinical evidence, blood serologic test *positive*)	14 1
Spontaneous "cure (no clinical evidence blood serologic test negative)	27 9
Died of syphilis other than cardiovascular or central nervous system	0 8
Died of some other cause (cancer tuberculosis, scattering)	23 6

The importance of these clinical observations cannot be over-estimated though it is improbable that similar studies can confirm them It is unlikely that anywhere else in the world does there exist, in as stable and easily followed a population as was that of Oslo, a large group of patients diagnosed as early syphilis by competent observers untreated, and reexamined years later with the expert care devoted to this series.

Taking the data at their face value, they indicate that of every 100 patients acquiring syphilis 23 will develop a late lesion which will incapacitate or kill 12 will develop a more benign late manifestation and 64 will probably pass through life unharmed, so far as they themselves are concerned It is a matter of small moment to these fortunate 64 whether necropsy performed after death from some unrelated cause reveals the presence of microscopic lesions of syphilis in various body tissues One criticism which might pertinently be raised by the pathologist is that syphilis may have been a contributory if not the direct, cause of death in the 23 per cent of Bruusgaard s patients who died from some other disease. This comment is at present unanswerable.

This summary of Bruusgaard s study is by no means intended to suggest that syphilis be allowed to pass untreated. The public health menace of transmission of infection to others would be a compelling reason for treatment even if modern chemotherapeutic advances had not altered completely the character of ultimate results. It does, however provide the physician with a healthy optimism as to the ultimate prognosis, which he is fully justified in passing on to his patient.

The Influence of Treatment on Prognosis

To what extent is the prognosis of untreated syphilis altered by treatment? We must first consider the possible effects of poor or insufficient treatment. It is a pertinent question to ask just what constitutes inadequate as compared with adequate treatment. To answer this in detail is the subject matter of this whole book, and only a very brief definition can be given here. The adequacy of treatment varies for different types of syphilitic infection and for each individual patient In general, it may be said that for early syphilis any treatment scheme is inadequate which does not include the use of a trivalent arsenical product to a total of at least 20 injections For late syphilis no such accuracy of definition is possible adequacy of treatment may vary between the time limits of a few months to many years For the average patient of either group no arsenical treatment, or a few injections only is obviously inadequate.

The effect of inadequate treatment varies according to the duration of syphilitic infection. In early syphilis a little treatment may be worse than none. In late syphilis this is probably not true. The explanation lies entirely in the fact that in early syphilis the patient s own resistance against the treponema is in the making, and until the secondary outbreak has spontaneously healed and latency is firmly established, is not complete. Prior to this time, the development of resistance may be interrupted by treatment one may do for the patient what, if left alone he would otherwise do for himself i.e., heal lesions and destroy treponemes If treatment

is stopped while foci of organisms remain in the body and the patient is left without defense against them, they may multiply *in situ* or be redistributed over the body as if freshly introduced from without. Under such condition infectious cutaneous or mucosal relapse is perhaps more common in early syphilis inadequately treated than untreated (cf p 24)

In addition to these types of relapse, most of which occur within the first two years after inadequate treatment, there has accumulated considerable evidence to indicate that the insufficient treatment of early syphilis may shorten the incubation period of late neurosyphilis. The studies of Frankl Hall Hopkins and Kemp and Menninger are in essential agreement and combined include a sufficiently large series of cases to permit accurate conclusions These observers agree that with the exception of acute syphilitic meningitis the incidence of neurosyphilis either

TABLE 7

AN ESTIMATE OF THE PROBABLE OUTCOME IN EARLY SYPHILIS UNTREATED POORLY TREATED, AND WELL TREATED

Type of syphilis		Probable outcome, expressed in approximate per cent, if—		
Original diagnosis	Ultimate outcome	Untreated	Inadequately treated	Thoroughly treated
Early syphilis	Serious late syphilis	25	35–40	<5
	Benign late syphilis	15	15	<2
	Latent syphilis	30	30	5
	"Cure"	30	15–20	85–95

clinical or asymptomatic, is not increased by the inadequate treatment of early syphilis. However the incubation period of late neurosyphilis (tabes paresis, and meningovascular neurosyphilis) is shortened by approximately 5 years in patients whose treatment for early syphilis was insufficient.

In late syphilis none of these calamities seem to occur Immunity the defense reaction is firmly established and is probably not impaired by treatment of any amount If treatment is interrupted short of the optimum there will be no such crop of immediate recurrences infectious or otherwise, and there is no evidence to show that the probability of development of late cardiovascular or central nervous system syphilis is any greater or the time relations between infection and their appearance any shorter than if the patient is untreated. Apparently the worst to be expected is that inadequate treatment may not halt the progress of the late lesion present and that continued progression rather than relapse may occur

Adequate treatment completely alters the picture It is generally agreed

that early syphilis is 'curable,' from biologic, symptomatic, and serologic standpoints, and that cure is more readily accomplished the earlier treatment is started. Thus in seronegative primary syphilis, approximately 100 per cent of "cures' may be obtained in seropositive primary and early secondary syphilis, from 80–95 per cent of 'cures " Here "cure" is used in all three senses, biologic, symptomatic, and serologic. The patients are well and remain well for indefinite periods of time. An estimate of how these results compare with those in untreated or inadequately treated groups of patients with early syphilis is provided in Table 7

The Prognosis of Special Types of Syphilis

In late syphilis, with biologic "cure" probably impossible, one is forced to rely on symptomatic cure"—"arrest —and serologic "cure.' We have attempted to estimate, for various types of late syphilis, approximately what may be expected in these two respects. We must emphasize that symptomatic ' cure is used in a different sense from symptomatic relief cure" meaning that not only does the symptom of which the patient complains disappear or the lesion heal, but that, in addition, he remains free from progression of that lesion or the appearance of new ones for the balance of his life. Thus in the data of Table 8, it is indicated that symptomatic "cure of aortic regurgitation or aneurysm is impossible, since sooner or later in practically every case the patient dies as the direct or indirect consequence of this lesion. Symptomatic relief however, is attainable in many such patients and life may be prolonged over a period of years far past the usual expectancy How little symptomatic and serologic cure" parallel each other may be seen in for example, bone syphilis, where symptomatic cure" is common, serologic "cure' rare or in tabes dorsalis where the reverse is true.

To offer a definite prognosis to a patient with late syphilis is hazardous without full knowledge of his physical status and, so far as the individual patient is concerned, is much more uncertain than in early syphilis in any event. Causes for caution are the frequent association of two or more types of late lesions, and the possibility that cardiovascular or central nervous system involvement may exist below the level of clinical recognition. It is convenient for prognostic purposes, as well as for others, to divide late syphilis into four main groups, i.e. latent, benign late, cardiovascular, and central nervous system.

The prognosis of latent syphilis is favorable, assuming that the probable association of cardiovascular syphilis has been ruled out as accurately as possible by physical and x-ray examinations, and that routine spinal puncture has shown the fluid to be normal. Few adequately treated patients will show clinical evidence of progression, though in late latency (after the fourth year) serologic negativity is not easily attained.

In benign late syphilis, with gummatous lesions of skin, mucosae bones, and joints, almost the same favorable prognosis may be given, provided again that associated cardiovascular or central nervous system lesions are absent. In this type of patient, there is more tendency than in latent syphilis to subsequent relapse of late lesions similar to those origi-

TABLE 8

THE PROBABILITY OF BIOLOGIC, SYMPTOMATIC, AND SEROLOGIC 'CURE' IN VARIOUS TYPES OF EARLY AND LATE SYPHILIS

Type of syphilis		Probability expressed in approximate per cent, if adequate treatment is given, of—		
		Biologic cure	Symptomatic "cure"	Serologic "cure"
Early	Seroneg. I	100	100	100
	Seropos. I	80–90	92–98	85–95
	Early II	80–95	92–98	85–95
	Recurrent II	70–80	80–95	70–80
Latent	Early	70–80	92–98	80–90
	Late	0	92–98	30–35
Benign late	Skin or mucosae	0	90–95	30–40
	Bones and joints	0	80–90	10–25
	Other organs	0	60–80	30–40
Cardio-vascular	Simple aortitis	0	70–80	30–40
	Aortic insufficiency	0	0*	30–40
	Aneurysm	0	0*	30–40
Central Nervous System	Early	0	70–90	65–95
	Diffuse late	0	60–80	30–40
	Tabes	0	20–35	60–70
	Paresis	0	15–30	0–10
Congenital	Early	80–95	85–100†	80–100†
	Late	0	0–80	10–20

* See text, pp 291 and 292.

† *Depending on age of the infant at the start of treatment (cf pp 507 509)*

nally present Residual scars are permanent. Certain late lesions are very occasionally resistant to healing notably naso-palatine lesions Involvement of the eye (most frequently kerato-iritis) often leaves permanent impairment of vision

Late visceral lesions (liver spleen stomach) are not mentioned in Table 8 largely because of their rarity as compared with the four major varieties of late syphilis The prognosis of each will be more fully discussed under the appropriate chapter heading. It may be said briefly that each is occasionally fatal either directly or indirectly (mortality about 10–20 per cent) that each usually leads to some degree even if slight of chronic impairment of health and that the chance of ultimate and complete recovery averages no better than 40–60 per cent.

Cardiovascular and central nervous system involvement are the major causes of adult death from syphilis. If cardiovascular syphilis can be recognized in the stage of uncomplicated aortitis before the development of aortic insufficiency or aneurysm the chance of symptomatic relief of permanent arrest of progress and of ultimate long life is excellent If

either valvular incompetency or aneurysm has developed, the average duration of life in untreated patients dating from the onset of symptoms, is only 12–24 months. With treatment, symptoms may be relieved in many instances, and life prolonged in relative comfort for several years at least.

The prognosis of central nervous system syphilis depends largely on the type of involvement present. It is always serious, so far as persistence of disagreeable or even crippling symptoms are concerned. In the case of paresis it constitutes a grave danger of life. Detailed discussion will be found in the chapters on the treatment of neurosyphilis.

As with acquired syphilis, the prognosis of congenital syphilis depends to some extent on whether the infection is recognised and treatment begun early or late. Untreated, infantile congenital syphilis is subject to a high mortality rate, which may be materially reduced but not entirely abolished by treatment. Late congenital syphilis is infrequently dangerous to life but may produce permanent disability in such vital structures as eye or ear. More detailed discussion will be found in the article by von Zumbusch and in Chapter XXVII of this book.

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Chapter IV

THE APPRAISAL OF THE THERAPEUTIC PROBLEM IN THE INDIVIDUAL PATIENT GENERAL CONSIDERATIONS AFFECTING PROGNOSIS AND TREATMENT

The treatment of syphilis is a problem which has steadily increased in complexity since the introduction of salvarsan more than 30 years ago. The better understanding of the course of the disease and of the high incidence of such late therapeutically difficult complications as cardiovascular and central nervous system involvement, the refinements of diagnostic technique the complexities of the laboratory procedures of complement-fixation and flocculation tests of blood and spinal fluid, the multiplicity of drugs available and the technical difficulties of their administration have all contributed their quota to the chaotic state from which syphilotherapy is only now beginning to emerge. It is true that many patients present therapeutic difficulties which tax the resources of the most accomplished expert, and which may even be insoluble. In the majority of instances, however the treatment of syphilis is a relatively simple procedure, as capable of satisfactory management by the physician in a rural community as by the expert.

Who should treat syphilis?—Success in treatment cannot be achieved by the physician whose view of syphilitic infection is limited to the presenting lesion which may fall into the domain of his particular medical specialty The urologist who looks no further than the chancre, the dermatologist whose knowledge of the infection is skin deep, the ophthalmologist whose physical examination is limited to a single organ is not the ideal syphilotherapist. This is not to say that interest in a special domain of medicine bars its practitioner from a thorough knowledge of syphilis. Among the leading syphilologic experts of the world are men whose basic training has been in pathology in internal medicine, in dermatology in neurology in pediatrics It is to say however that to be successful in the management even of the simpler uncomplicated problems of syphilotherapy the physician must have a basic knowledge of the biology clinical course, and pathology of syphilitic infection, which in it self implies a fairly wide acquaintance with general medicine. For some of the complex situations which may and often do arise, all rules of thumb go by the board, and the treatment of syphilis becomes an art which only those with wide experience should attempt to practice.

The Necessity for Preliminary Study of the Patient

The first prerequisite for the physician who attempts the management of syphilis is the ability to view his patient as a human being. This implies the ability to perform and properly to interpret a general physical examination. It is better both for patient and physician, if this can be done by

the one who is directly in charge of the patient. If owing to his greater interest in some more highly specialized domain of medicine, the physician has lost familiarity with the interpretation of heart sounds, with palpation of the abdomen, with ophthalmoscopic examination, he must be prepared to get his information secondhand and to refer his patient for a general survey to a competent syphilologist or internist. *But a complete examination must be made before treatment is started.*

There are several cogent reasons for this insistence First of all, it is important to know what damage syphilis has done to the patient. The examination limited to inspection of and darkfield examination of the serum from a penile sore to a description of skin lesions to palpation of a diseased joint, is inadequate. Syphilis is a disease which may involve almost any structure in the body The type of treatment employed will often vary depending on the organs or systems involved and the extent of the damage Many a patient has been treated for supposedly latent syphilis, involvement of the nervous system or heart and aorta having been missed because it was not looked for with the result that valuable time and money have been wasted, and in some instances, a successful outcome missed.

Second complete examination is necessary in order to detect or to rule out the presence of complicating diseases, which may alter the patient's reaction to syphilitic infection or his ability to tolerate treatment for it There are several common afflictions of mankind which fall into this category notably tuberculosis, nephritis diabetes, hypertension, and arteriosclerosis In a patient with both syphilis and tuberculosis, one is faced immediately with the public health issues and the relative prognostic importance of each infection as well as with important problems of drug therapy When nephritis complicates syphilis it may be necessary to carry on treatment without the aid of the heavy metals.

Next, it must be remembered that the arsenical mercurial and bismuth drugs used in syphilotherapy are poisons, and that he who undertakes to administer them to a patient with whose general physical status he is not conversant, runs grave risks. Patients have died after a single injection of arsphenamine because of the physician's lack of knowledge that cardiovascular syphilis was present. Others with a previously existing but unrecognized chronic nephritis, have been made into hopeless invalids by the injudicious use of bismuth or mercury

Last, but not least important, is the value of the original physical examination in setting up a base line for measuring possible progression of the syphilitic infection in after years. In order to determine the fact of "cure" periodic physical examination is essential in all treated syphilitics Subsequent progression is to be feared chiefly in cardiovascular or central nervous system. Obviously unless one has records of cardiac measurements of blood pressure of the equality regularity, and reacting properties of the pupils of reflexes, of the color of the optic discs etc., at the time of the original examination, one is at a complete loss to interpret such changes as may later appear

It is not within the province of this book to discuss the technique of

physical examination. The minimum requirements for success in syphilotherapy are comprised within the term "general medical examination," in which special attention is paid to the heart and great vessels, to the nervous system and to the fundus of the eye. Indispensable preliminary laboratory examinations are routine examination of the urine and a blood test, the latter to be used as a base line for measuring serologic progress.

The Factors Influencing the Patient's Response to Treatment

Four important factors enter into the response to treatment of any patient with syphilis. These are (1) the patient himself (2) the invading parasite (3) such collateral influences as intercurrent infection, pregnancy alcoholism, etc., and (4) drugs Only the last of these is actually within the power of the physician to control. The others he can at best attempt to evaluate, and on the basis of his appraisal, adjust his method of specific therapy to them.

The patient his constitutional background —The preliminary examination on which so much insistence has been laid gives the physician an idea as to his patient's physical status, but tells him nothing of his constitutional and immunologic background. Recent studies (Draper) suggest that both of these may be factors of importance in his resistance to disease processes of all sorts In addition to a complete story of the syphilitic infection, therefore, the careful physician will want many anamnestic details useful in his appraisal of his patient as a living organism. It would be desirable, from the standpoint of syphilis and its prognosis and treatment, to have information concerning the longevity of the family the patient's resistance or lack of it to other infections, and the presence or absence of a tendency to allergic diseases (asthma, hayfever eczema) in the patient or his family Longevity is a distinctly hereditary factor which materially influences life expectation and which must therefore be considered in offering a prognosis to the patient with syphilis. Resistance or lack of it to acute infectious diseases is a constitutional factor perhaps dependent on hereditary influences, perhaps on unknown peculiarities within the patient himself It does not necessarily follow of course that because the patient has had severe attacks of more than his share of *children's diseases* he will behave similarly if he develops syphilis the exquisite example of chronicity among infections. It is at least suggested, however that the constitutional and immunologic background may have much to do with his ability to deal with syphilis. An allergic tendency is important in its relation to syphilotherapy sensitization to the arsphenamines being one of the untoward effects of treatment. Whether this tends to occur more frequently in patients with an already existing allergic instability is as yet unknown, but it is a point deserving of notice.

The influence of race —Other factors entering prominently into an appraisal of the individual patient are race, sex, age, and economic status. Syphilis tends to follow certain definite disease patterns in different racial stocks. This difference is not particularly apparent as between members of the various Caucasian peoples, most of whom proceed either from an

ethnologically identical source or are so intermingled that no clean-cut distinction is possible. It is striking, however, as between whites and Negroes (Turner) The latter tend to develop as part of the secondary outbreak, folliculo-papular and annular types of rashes and an extensive generalized lymphadenopathy, less frequent in the white In late syphilis, the Negro is particularly prone to the development of bone or cardiovascular lesions (twice to four times as often as in the white), and much less likely to develop central nervous system syphilis, especially tabes and paresis, than the white. These are factors of importance in estimating the patient s reaction to his infection.

The influence of sex —Sex exerts an even more striking influence on the course of syphilis which as has been pointed out for years is a much milder disease in women than in men Although in the past this has been ascribed to the beneficial effects of pregnancy recent experimental studies (Frazer Kemp and Shaw) have shown that the female sex hormones are probably equally responsible. The beneficial effects of preg

TABLE 9

THE RACE AND SEX INCIDENCE OF VARIOUS SYPHILITIC LESIONS
(After Turner)

Type of lesion		Percentage frequency in			
		Whites		Negroes	
		Males 2213 cases	Females 1225 cases	Males 2804 cases	Females 3758 cases
Early syphilis involving †	Eye	3 5	1 9	9 5	4 8
	Skeletal system	0 4	0 6	3 1	1 7
	Nervous system	6 4	2 8	3 1	1 7
Late syphilis involving ‡	Skin and mucous membranes	7 8	11 6	9 0	8 3
	Bones and joints	6 0	5 8	12 6	8 6
Cardio-vascular syphilis	Aneurysm	1 2	0 8	3 0	0 7
	Aortic insufficiency	2 8	1 4	5 0	1 5
	Aortitis and other forms	4 7	3 1	9 9	5 0
Neuro-syphilis	Paresis	8 4	5 0	2 0	0 3
	Tabes	13 9	4 6	3 5	0 8
	All other	17 0	12 6	10 4	5 9
Latent syphilis		40 3	55 9	41 5	66 4

The incidence of some lesions in which there are no striking race or sex differences is omitted.

† In this group, the percentages are expressed in terms of the total number of patients with early syphilis.

‡ In this and following groups, the percentages are expressed in terms of the total number of patients with late syphilis.

nancy are most apparent in the early stage of the disease. If infection with syphilis and impregnation coincide, all the customary lesions of early syphilis are usually conspicuous by their absence. The patient presents no obvious evidence of infection except a positive blood serologic test. As a matter of fact, she may go for years after infection with no obvious signs, and indeed, syphilis may so far as she individually is concerned prove to be a perfectly banal infection (Moore) This makes her none the less a public health menace, so far as the transmission of disease to other adults or to the product of conception is concerned and it increases enormously the difficulties of recognition of syphilis in the female as contrasted to the male. The routine blood serologic test is the only way in which the majority of female patients with syphilis can be recognized, and it should be employed as freely as urine testing in every general medical examination and in every pregnant woman. The influence of sex in estimating the probable outcome of syphilis must be given due consideration.

The data justifying these statements as to the influence of race and sex in modifying the course of syphilis are presented in Table 9 They are modified from a study by Turner of the admission diagnoses of 10 000 consecutive syphilitic patients in the Syphilis Division of the Johns Hopkins Hospital.

The influence of age —The age of the patient enters prominently into an appraisal of the possible effects of syphilis on himself and into a consideration of the desirable form and amount of treatment. The prognosis of a recent infection is obviously vastly different in the youth of 20 and in the senile man of 70. The one, with his life nearly ended, need not fear the possible development of aneurysm, tabes, or paresis. The other with a life expectancy of 50 years, must be energetically treated to prevent disaster to himself In both, however the dangers of transmission of the infection to others demand treatment, regardless of the individual issue involved. If late lesions of syphilis are present at any age, some treatment will probably be essential for symptomatic relief if for nothing else. Whether it should be energetic or prolonged will depend in many patients on a weighing of the several issues of age life expectancy physical status, and the probability of the transmission of infection to others. There is not the least convincing evidence, however that, *per se*, syphilis contracted by the individual over 60 years of age is more severe than in younger individuals. The young man or woman in good health and within the procreative period is obviously in a different case from the individual of 60 or over whose sexual life is nearly or completely finished and whose remaining years afford little time for the development of crippling or fatal lesions. The patient with latent syphilis is a problem unto himself, which will be given due consideration in a separate chapter

The invading organism —If the patient s tissue reaction to the invading organism is almost wholly beyond the control of the physician, such factors as virulence and strain of the parasite are even more so. It is probably true that both in human beings and experimental animals the virulence of strains of *T pallidum* may differ Whether this is on the basis of inherent differences in the organism, or on such factors as size of inocu-

him, is not clear and indeed there is little experimental proof to back up the basic statement. It is an old clinical observation that there seems to be a strain of treponemes particularly prone to attack the nervous system, especially the marital partners of tabetics and paretics (Moore and Kemp) and the offspring of such individuals (Kemp and Poole) This is also suggested by the frequency with which neurosyphilis may appear in each of several individuals infected from the same source. Attempts have been made to confirm these observations experimentally without clear cut success. Reasoner reported working with a strain of treponemes which was particularly prone to produce chorioretinitis in the rabbit. Thus far this work is unconfirmed. Levaditi and Marie believed that they could *distinguish definite neurotropic and dermotropic strains* but as Jahnel points out, it seems probable that their so-called neurotropic virus was confused with *T cuniculi* the organism of spontaneous rabbit spirochetosis. Plaut and Mulzer have worked with a strain which causes pleocytosis in the spinal fluid of rabbits in a much higher proportion of cases than other strains but it is not entirely clear that they have controlled the confusing factor of spontaneous encephalitis in rabbits and their work has not yet been confirmed Others have attempted without success to show that the strains of organisms concerned in malignant syphilis of human beings, and also so-called arsphenamine-resistant strains retain these properties when transferred to rabbits One method of clinical approach to the problem which has not as yet had the attention it deserves is a study of the course of syphilitic infection over a period of years in a large series of husbands and wives, presumably infected with the same strain (O'Leary) The evidence as to the existence of special strains of organisms with predilection for certain body structures is therefore incomplete and for the present we must render the Scotch verdict of not proven To the authors it seems probable that the course of infection in any given patient depends much more on factors inherent within himself than in degrees of virulence in the organism.

Collateral Influences—Certain of the collateral influences affecting the course of syphilis or its response to treatment have already been mentioned. The association of tuberculosis and syphilis seems in some intangible manner to be of favorable import, or at least not markedly unfavorable for each disease. This relationship may be markedly disturbed by treatment As the tuberculosis gets better the syphilis may get worse and *vice versa*. Treatment for syphilis sometimes seems to exercise a particularly deleterious effect on tuberculosis as will be discussed in detail later Arteriosclerosis of the aorta and hypertension may act as a predisposing element in the etiology of syphilitic aortitis. Nephritis arteriolar sclerosis and hypertension may modify the patient's tolerance for antisyphilitic drugs.

The influence of acute intercurrent infections is more difficult to evaluate. Certainly there is no clear-cut evidence in syphilis as there is in tuberculosis, that an acute infectious disease occurring in a patient with a quiescent or latent infection stirs the more chronic lesion into renewed activity There is nothing in syphilis to parallel the flare-up in an old tuberculous

pulmonary lesion following an acute upper respiratory infection. There is some evidence, however, that chronic focal infections in teeth, genito-urinary tract or elsewhere may cause exacerbations in certain symptoms of syphilis, notably in the lightning pains of tabes

Pregnancy is certainly one of the most important natural extraneous influences on the course of syphilitic infection. As already pointed out, if impregnation and infection with syphilis approximately coincide, the lesions of early syphilis may be completely suppressed or failing this, the usual time relations between the early and late lesions of syphilis may be markedly distorted (Moore) Thus there may be an interval of many months instead of a few weeks between primary lesion and secondary outbreak or precocious tertiarism may develop. In general, however, the effects of pregnancy are beneficial so far as the mother's syphilis is concerned. Whether this benefit may be gained from pregnancies occurring sometime after infection is as yet not evident. The mechanism of this action is unknown. Some years ago Moore suggested that it might be the explanation for the much lower incidence of neurosyphilis in women than in men, and Solomon has expressed the same idea. More recently Kemp and Menninger have shown that neurosyphilis is less frequent in women who have not experienced pregnancy after infection than in men. The probable reasons for this have been discussed earlier in this chapter In certain instances of syphilis in women, pregnancy may even be used as a therapeutic procedure if the patient understands that treatment must be continued without intermission during pregnancy if she is willing to co-operate, and if she accepts the small risk of the birth of a syphilitic baby even after adequate treatment.

The influence of alcoholism on the course of syphilis cannot be evaluated, but except in so far as the excessive use of alcohol induces general irresponsibility and a tendency to uncooperativeness in treatment, we do not believe that it is very great, time-honored tradition to the contrary notwithstanding.

Drugs —The influence of drugs in the control of syphilis will be discussed in subsequent chapters.

The mental reaction of patients to syphilis and its treatment —In the minds of many patients, a sense of shame of disgrace, accompanies the knowledge of infection with syphilis. The patient feels himself outcast, unfit to associate with normal persons he is confused as to infectiousness refraining from the ordinary daily contacts of life for fear of transmitting his disease to others. Each visit to the physician may be the source of spiritual agony to be carried out furtively and under cover, with coat collar turned up and hat pulled down. A genuine anxiety neurosis may develop the patient feels that his whole future life is blighted and that he is forever barred from normal society The physician may do much to alter this mental attitude, to enable the patient to adjust himself to his misfortune. Preaching and moralizing are taboo the patient must be made to realize that syphilis is a disease not a sin that the physician is interested in health not in morals that if treatment is properly carried out, any of the normal relationships of life are possible including mar-

riage and the facts of infectiousness must be carefully explained. Psychotherapy is often as important as antisyphilitic treatment.

With all patients reading about the disease should be forbidden. A little knowledge is a dangerous thing. Every physician, recalling his student days, can remember that he suffered (in mind) from many of the diseases he studied. The syphilitic patient must be protected against too detailed and graphic a knowledge of the late sequelae of the infection.

The over treatment syndrome—Partly because of inability to adjust himself mentally to treatment, partly for actual physical reasons the occasional patient may after some weeks or months of therapy become irritable, emotional, and increasingly nervous over each visit to the physician he may begin to lose sleep appetite, and weight. As has been recently re-emphasized by Cormia, encouragement, careful re-evaluation of the patient's therapeutic problem and a short rest period will do wonders in this situation.

The Influence of the Economic Status of the Patient

One of the most important, and the most frequently dodged issues of syphilotherapy is the economic status of the patient. Most individuals contract syphilis when they are young, at a time when their earning capacity is at a minimum. As soon as the diagnosis is made, advice is given as to treatment which may be as impossible of fulfillment as the advice to the tuberculous pauper to transplant himself from Maine to Arizona, to take a dozen eggs a quart of cream and a toddy of sherry daily Under any circumstances, the treatment of syphilis is a costly business. For the average patient with uncomplicated early syphilis the total cost of adequate treatment under conditions of clinic practice (The Johns Hopkins Hospital) is $78 The prevailing minimum fees of private practice ($5.00 for an injection of an arsenical drug, $2.00–2.50 for an injection of bismuth, with free serologic service from the Board of Health) bring this up to a minimum of $350 00 spread over a period of 15 months. These are minimum fees the average charge for private care is nearly twice as great. If instead of early syphilis the unfortunate patient has tabes with optic atrophy paresis, or any one of a dozen complications of late syphilis necessitating hospitalization or special treatment procedures, or if more than one member of the family must be treated as is only too often the case, the cost of treatment mounts to staggering proportions Many a patient, unable to meet the financial drain and too proud to go to a free or semi-free clinic, has abandoned treatment, with the result that ultimate disaster has overtaken him or his family It is currently estimated that about 80 per cent of the population cannot pay for adequate care of syphilis at private rates that about half of the population could meet the prevailing fees of pay clinics and that at least one-third, if infected must receive treatment free or for nominal amounts. The cost of treating the disease is an important cause of the insufficient or inadequate treatment which many infected persons receive.

Those physicians who undertake the treatment of syphilis have a threefold duty to perform in the solving of this problem and—the straws in

the wind are clear—failure to solve it means that the problem will be taken from the hands of the medical profession by outside sources with state medicine as the forced alternative. The first requirement is a frank discussion with the patient of what will probably be required in the way of treatment, how much it will cost and how it is to be paid for Next, if agreement cannot be reached between patient and physician, or if believing himself able to stand the financial burden at first, the patient's circumstances alter so that he is unable to continue, the duty of the physician is imperative to make some arrangement for a continuation of treatment either at the hands of a colleague whose fees are not so high, or at a free or semi-free clinic. Treatment must never be abandoned because the patient is unable to pay for it. Finally, the physician must adjust his therapy to the patient's ability to carry it out, must weigh therapeutic benefit against cost. For example, two months administration of mercury by inunction will, if properly carried out, accomplish about as much and at far less expense than a series of 30 daily intravenous injections of a soluble mercurial salt. Equally striking examples may and will be pointed out in the later sections of this book.

The establishment of pay clinics by the initiative and under the control of physicians themselves is an important forward step which, however will not solve the problem entirely What is worse needed is recognition by the private practitioner that the economic issue does exist, and the maintenance of the personal relationship between himself and his patient by a frank and mutual facing of the facts.

The follow up of patients —An indispensable feature of the clinic is the social service worker, one of her most important functions is follow up, the holding of patients to their task. In private practice the physician must assume this phase of the social worker's duties. Patients with early syphilis who fail voluntarily to carry out the prescribed routine must be followed first by the physician's own effort, and if this fails, by the authorities of the local Health Department. A personal letter to the lapsing patient with late syphilis will often permit the administration of adequate treatment. When treatment is finished, yearly letters of inquiry will remind the patient of the desirability of periodic survey and will enable the physician to evaluate the results of his therapeutic efforts. A systematic system of follow-up is of as much value in the private office as in the public clinic.

The treatment of the peripatetic patient —The exigencies of earning a living demand that some individuals, especially travelling salesmen and actors, spend the major part of their lives in transient living. Should such a person be unfortunate enough to acquire syphilis, he usually encounters considerable difficulty in receiving proper treatment for it. Forced to consult a series of physicians he is subjected to changes in type or manner of treatment, to varying degrees of expertness in its administration, and to differences of opinion, sometimes legitimate, sometimes born of ignorance as to what should be done Only too often these differences of opinion are laid before the patient, with the result that he is hopelessly confused as to his proper course, and often so discouraged by

the seeming lack of agreement between physicians that he abandons further therapeutic efforts

There is an easy and perfectly satisfactory solution for this problem. The physician who inaugurates treatment should provide the patient with a series of documents including (1) a copy of his history and the record of his physical examination, to spare him the necessity of repeating this in detail to each new physician (2) a written outline of treatment, planned as definitely as possible with dates drugs, and dosage for several months in advance, and to be followed, barring unforeseen complications, by each of the physicians who sees the patient (3) the name and address of a physician in each town (secured from the American Medical Directory) on the patient's itinerary, together with a blanket letter of introduction. This letter should specify the fee which the patient is able to pay for various treatment procedures.

This system retains the management and direction of the patient's treatment, and the responsibility for the ultimate outcome, in the hands of a single physician, where it properly belongs It is assumed that the directing physician is competent to direct and carry out antisyphilitic treatment. Even if he is not, it is often true that bad advice from a single source is better than conflicting good advice from many sources.

The duty of the various physicians to whom the patient may be referred is plain. They must carry out exactly the treatment procedure which the directing physician has indicated unless of course some unforeseen complication makes this impossible. The treatment given should be recorded as to date and dosage on the record to be retained by the patient, and returned ultimately to the original physician. No comments of any sort as to the suitability of treatment or the competency of other physicians should be made to the patient, nor should the details of his case be discussed with him If he insists on asking questions, he should be told to consult his original physician, either in person or by mail. If a change in the planned outline of treatment is essential for any reason it should be made but the original physician should be notified at once of the alteration and the reason for it. In other words each physician no matter what his professional eminence or particular expertness, should regard himself as the temporary assistant of the physician primarily responsible for the management of the patient, and should conduct himself accordingly

Occasionally one encounters patients whose business takes them to small remote communities where special drugs necessary for their treatment are not available. Under such circumstances it is perfectly justifiable for the physician to furnish these drugs to the patient to take with him They should be accompanied by a letter explaining in detail the method of administration the untoward reactions that might be expected and the management of the patient should they occur Much of the responsibility for the management of such a case rests with the patient, and he as well as the physician under whose care he is at the time should be instructed to communicate immediately with the physician who is directing his treatment should anything untoward happen

The function of the expert in syphilotherapy —What is the re-

lationship which the expert syphilologist should bear to practitioners of medicine and to the great mass of patients with syphilis? It is obviously impossible for all patients to be treated by specialists though the surveys of venereal disease prevalence carried out by the United States Public Health Service indicate that in urban areas the trend is in this direction. In most large cities, the majority of syphilitic patients are under treatment in special clinics or in the hands of a few private practitioners In smaller communities and in rural areas, this is both impractical and undesirable. It is the proper function of the expert, with the clinical material at his disposal, to study the applicability of treatment methods, to evaluate the results obtainable from them, and to present them to the practitioner in a fashion which makes them largely applicable to routine office practice even in the smallest communities. In two-thirds of the syphilitic patients encountered in a large general hospital, treatment is a relatively simple matter which any well trained physician should be able to carry out.

In addition to this however the expert has three other important functions. He may and should serve in the capacity of a consultant for the physician who wants to provide his patient with the best available treatment at the lowest possible cost. The syphilologist may develop the plan of attack to be carried out by the practitioner For example while it is obviously out of the question for a patient in a small town to make weekly visits for treatment to a large city 500 or perhaps only 50, miles from his home he may be able to afford two such visits a year At the first visit he may be thoroughly studied and returned to his local physician with recommendations for treatment covering the next six months. Even in the simplest case, that of early or latent syphilis, it is rarely possible to plan treatment in detail for more than six months too many unforeseen contingencies may enter the picture. At the second visit, six months after the first, the results of treatment so far given may be evaluated, the physical and laboratory status rechecked, and the patient again returned with advice for further treatment. Periodic surveys of this sort by the consulting syphilologist are inexpensive, may serve to solve perplexing problems of treatment, aid in safeguarding the future of the patient and his family and help the family physician to share the responsibility of possible progression or relapse. This sort of cooperation between practitioner and specialist is particularly desirable in patients with late syphilis or when complications of treatment arise indeed, in these circumstances such a division of responsibility is almost essential if the patient is to get the best results from treatment.

A second function of the expert is in the administration of special forms of treatment beyond the facilities or experience of the practitioner Examples in point are subdural treatment (intraspinal or intracisternal injections) and fever therapy neither of which should be attempted by the physician without previous thorough training, and without the facilities of a well equipped hospital.

Finally the syphilologist has a legitimate interest in the direct management of the many complex treatment problems so frequent in late syphi-

problem has recently been restudied by Eagle, who in a series of experiments adequately controlled by animal inoculation has demonstrated that all the trivalent arsenical drugs in use at the present time exert a very marked treponemicidal action *in vitro*, as do also soluble salts of bismuth. He found that depending upon the drug and the conditions of the experiment, treponemes were killed in dilutions of arsenical compounds ranging from 1–250 000 to 1–4,700 000 i e. in concentrations approximately *equivalent to those encountered in the body after the administration* of usual therapeutic doses. (The treponemicidal activity of bismuth compounds *in vitro* will be discussed in Chapter VIII)

The toxic effects of drugs used in the treatment of syphilis are not so simply explained. They cannot be accounted for as Kolmer emphasizes, on the simple basis of union of chemical with all body cells or those of special organs but may be produced in a wide variety of ways involving complex physicochemical effects of blood and body tissues. Some of these, so far as the arsenical preparations used in the treatment of syphilis are *concerned are fairly well understood as will appear in Chapter VII* dealing with the complications of treatment others are still obscure.

The new science of chemotherapy applied to the treatment of syphilis has produced a whole series of new arsenical drugs and a completely new set of compounds of bismuth. Many of these have been carefully studied, usually by one of the groups of investigators mentioned above, and have won a firm place for themselves in the actual treatment of patients. Many others unfortunately have been introduced into human therapy by careless investigators or venally minded pharmaceutical houses, without ade*quate preliminary investigation in animals. The widespread adoption by* physicians of drugs of this latter type on the basis of seductive advertising or the persuasion of the detail man, has resulted in enormous harm to patients. How can the physician tell whether a drug recommended for the treatment of syphilis is actually worthy of his adoption? There are certain definite criteria which should be fulfilled.

1 *Chemical constitution.*—The chemical constitution of the drug must be actually or approximately known the process of its manufacture described and this information published for the benefit of the entire medical profession. Secret proprietary remedies are beyond the pale of reputable syphilotherapists.

2. *Toxicity tests* —The toxicity of the drug for lower animals and by various routes of administration must have been thoroughly investigated. The animals usually employed are mice, rats and rabbits and the toxicity of the drug expressed in terms of the maximal *tolerated dose—milligrams* of the drug per kilo of body weight (mgm/kg) of the test animal

3 In addition, *histopathologic studies* of the internal organs of test animals, treated with lethal and with average therapeutic doses of the drug, must have been made. The latter is essential in order to guard against the possibility that slowly progressive anatomic and physiologic damage may have been done (to liver or kidneys for example) although the animal may have survived the acute toxic effects of the drug.

4. In addition, these essential data may and should be supplemented

by studies in animals of such factors as rate of excretion, rate of absorption from depots of intramuscular injection and effect of the drug on important organs (as for example the predilection of toxic effects for the central nervous system as manifested with certain pentavalent arsenicals by the development of the waltzing phenomenon in mice)

Such *toxicologic studies* are not directly translatable to human beings, but they afford a rough estimate of the danger of clinical use of the drug in question They must be supplemented by early observations of toxic effects in man. The arsphenamines produce in man four serious types of reaction dermatitis, jaundice blood dyscrasias, and hemorrhagic encephalitis, not observable in test animals and in the case of one arsphenamine product, sulpharsphenamine, the high incidence of dermatitis (together with certain other toxic phenomena), unpredictable from the animal studies, has led to its practical abandonment in acquired syphilis of the adult.

Furthermore low toxicity is not necessarily the most desirable feature of a drug. It is possible with certain products, by means of slight chemical alterations in the method of manufacture, to reduce toxicity enormously but unfortunately therapeutic activity may also be so reduced as to render the substance worthless.

5 *Tests of therapeutic efficiency*—Elaboration of the studies of Eagle heretofore mentioned will undoubtedly simplify present methods for testing the therapeutic efficiency of antisyphilitic drugs. However until these studies are completed, it is necessary to evaluate such preparations according to their efficiency in the treatment of experimental syphilis in the rabbit and by tests for their trypanocidal activity

Rabbit syphilis. It is possible in the rabbit to study the disappearance of surface organisms, the rate of healing of lesions and, by means of lymph node and tissue transfers to normal animals, the actual sterilization of the infection. The results should be expressed in terms of the smallest single dose (in milligrams per kilogram) capable of sterilizing the experimental animal thus permitting, when compared with the maximum tolerated dose an expression of the therapeutic index.

This type of study is time-consuming, requiring several months for completion, costly and not exactly translatable to human syphilis, in the sense that since syphilis in the rabbit is easier to cure than syphilis in man the optimum dosage in the rabbit is not capable of direct application in clinical practice with equal prospect of success. But it provides information so valuable especially as concerns the relative worth of different drugs, that it must be carried out with every new product proposed and should be carried out from time to time for routine testing of *fresh lots of various drugs already in actual use* to make sure that their therapeutic potency is maintained.

6. *Tests of therapeutic efficiency Trypanocidal tests.*—Ehrlich's original work as to the therapeutic efficiency of the products he studied was carried out on trypanosome infections in rats and mice. Such tests afford a valuable but rough index of treponemicidal activity as well that is an arsenical drug which has a high therapeutic index in trypanosome infec-

tions will also be possessed of treponemicidal activity That the approximation is only rough, however has been shown by various investigators, notably Brown and Pearce and Kolmer The ratio of trypanocidal activity to treponemicidal activity varies with different arsenical preparations between 1 1 and 1.5 Bismuth preparations, which exert a considerable treponemicidal activity have no trypanocidal effect. The advantages of the method are that, as compared with rabbit syphilis, it is cheap and quickly conducted, an answer being available in days instead of in months, and the end results are sharply defined. Trypanocidal tests cannot serve as a substitute for therapeutic testing in rabbit syphilis but tests in both infections should be carried out, and once the substance has been demonstrated to have treponemicidal activity its stability and the continued *potency of subsequent lots may be checked by repeated trypanocidal tests.*

7 *Clinical trial.*—Finally, before being released for general distribution, a drug which has successfully passed through these various phases of animal experimentation must be subjected to careful clinical study in a large series of patients under expert control. This type of clinical testing is preferably carried out *in at least two* large centers, not by distribution of the drug to a dozen or so physicians for trial in a few patients in private practice. It involves a long study in which a number of factors must be controlled. Roughly comparable groups of patients should be chosen, and treatment must be started with the test drug not used in association with any other in order that an isolated estimate of its efficiency may be made. Before it is tried in the treatment of early syphilis the rate of healing of measurable lesions of late syphilis should be determined (Snodgrass) If it proves satisfactory in this regard a trial in patients with early syphilis is justified. The factors which must be determined in evaluating the efficiency of a test drug have been outlined by Moore as follows

1 The rate of disappearance of surface organisms from the moist lesions of early syphilis.

2. The rate of healing of visible early and late lesions (or of symptomatic response in such conditions as neurosyphilis)

3 The rate of reversal of serologic reactions in early syphilis.

4. The proportion of serologic resistance i.e. Wassermann fastness, in early and late syphilis.

5 The incidence of abnormal spinal fluids in treated patients with early syphilis.

6. The incidence of serologic relapse in early syphilis.

7 The incidence of early clinical relapse, especially infectious mucocutaneous relapse and neurorecurrence.

8 The incidence of late progression or relapse.

9 The permanence of clinical and serologic normality

10 The incidence of toxic reactions.

The first of these requirements may be determined in a few days the second and third in a few weeks the fourth, fifth, sixth, seventh and tenth in a few months but the eighth and ninth require literally years of study and observation If a drug proves satisfactory in all requirements except the eighth and ninth, it may be released for general use.

In our judgment, the study of a new drug may involve the treatment of at least 100 patients and a year of time before even a tentative opinion can be expressed as to its probable acceptability A final opinion as to its value is a matter of many years of study in thousands of treated individuals and is something which cannot be rendered in the case of any antisyphilitic drug with the possible exception of arsphenamine itself

8. *Acceptability to the Council on Pharmacy and Chemistry of the American Medical Association.*—Last of all, and prior to marketing by means of the usual advertising campaign, the new drug should have been submitted to and accepted by the Council on Pharmacy and Chemistry of the American Medical Association. This implies that the statements of its proponents have been checked by disinterested observers and that the manufacturers sponsoring it do not claim extravagant virtues for it.

The drugs to be discussed in the following chapters on the arsphenamines, bismuth, mercury, and the iodides, have met and passed all these requirements. No others will be given attention in this book, and the practicing physician is strongly urged not to use any drugs in treating patients with syphilis which do not conform to these qualifications.

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Chapter VI

THE ARSPHENAMINES, THE ARSENOXIDES, TRYPARSAMIDE

Salvarsan the six hundred and sixth drug of the series studied by Ehrlich and his co-workers first came into wide-spread use in the treatment of syphilis in 1909–1910 Since then, the literature describing its chemistry, toxicity, and therapeutic activity in animals and man has reached proportions so vast as to defy review The reader desiring detail may consult Kolle and Zieler's monograph, which covers the literature to 1924 or various articles in the new edition of the *Handbuch der Haut und Geschlechtskrankheiten* which brings the bibliography closer to date Here an attempt will be made to compress into short space those essential facts which the practitioner should know

Since the original success of salvarsan numerous arsenical drugs chemically allied to or derived from it have been introduced, with the hope of improving therapeutic efficiency of reducing toxicity or of eliminating some of the technical difficulties of administration. Many of these highly lauded at first, have been abandoned after more extended trial Certain others, however have made a place for themselves in syphilotherapy and will also be considered in this chapter These are neoarsphenamine silver arsphenamine sulpharsphenamine tryparsamide, bismarsen and mapharsen Brief mention will also be made of neosilverarsphenamine and of stovarsol. Other arsenical drugs than these have either been abandoned as worthless, or are still in the experimental stage, and no effort will be made to describe them

Incidentally it should be noted that during the first World War the *German patents on salvarsan and its derivatives were abrogated in the* various allied countries. In the United States they were taken over by the Chemical Foundation the patented name salvarsan was replaced by the generic term arsphenamine " and various American manufacturers were licensed to make these drugs Thus American-made arsphenamine is identical with Ehrlich's 606 " neoarsphenamine with '914 " etc The trade names of various manufacturers for these preparations differ slightly The manufacture of these drugs is supervised by the National Institute of Health, Washington D C (formerly Hygienic Laboratory) under the control of the United States Public Health Service in the sense that minimum standards of toxicity for animals are required and that the statements of the manufacturers in this respect are checked by toxicity tests carried out at the National Institute of Health.* Unfortunately therapeutic efficiency is not controlled by the United States Public Health Service and in this respect the manufacturers themselves

* However mapharsen and tryparsamide which are not strictly speaking members of the arsphenamine series are not so controlled

must be relied upon for frequently repeated trypanocidal or treponemicidal tests of new lots of drugs, which are too rarely carried out.

Arsphenamine.—The chemical base of arsphenamine is 3,3-diamino-4,4 *dihydroxyarsenobenzol*, *marketed as the* dihydrochlorid salt. In this form, the drug is an amorphous yellow powder with a slightly greenish tinge, slowly soluble in cold water It contains about 31 per cent

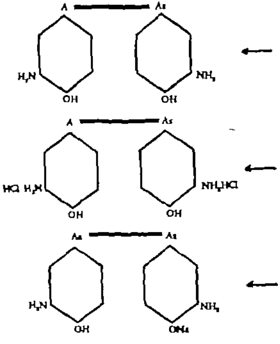


FIG 5.—This is arsphenamine base, *insoluble* in water To achieve solubility and chemical stability it is marketed as the dihydrochlorid. This preparation is soluble, but is too toxic for use. When enough NaOH solution is added completely to pre*cipitate and then to redis*solve, there is formed the *monosodium salt*. Some physicians use this for intravenous injection, but it is slightly more toxic than the disodium salt, which is prepared by adding approximately ½ excess of alkali (see specific directions) or 0.85 cc. of 4 per cent NaOH for each 0.1 gram of the original dihydrochlorid.

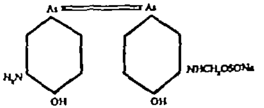
arsenic. The acid salt is too toxic to administer and must be alkalinized before use. When alkali is added the insoluble arsphenamine base is first precipitated then redissolved. At the point of re-solution the monosodium salt is formed. If a slight excess of alkali is added one obtains a mixture of the mono- and disodium salts, and in this form the drug is least toxic and causes less irritation to the veins. The toxicity of these three forms of the drug for rats, in terms of milligrams per kilo of body weight, is, according to Kolmer

Actually the disodium salt is not formed until ½ excess of alkali has been added. This, however is too alkaline for use and the above combination of the mono- and disodium salt is recommended.

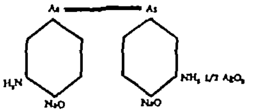
Acid solution	10–20 mgm/kg.
Monosodium salt	120–140 mgm/kg.
Disodium salt	140–150 mgm/kg

The chemical steps involved in this change from dihydrochlorid to disodium salt are shown in Fig. 8. Arsphenamine is slowly oxidized on exposure to air and is therefore marketed in ampules in which a vacuum has been created or which have been filled with an inert gas (usually nitrogen) The oxidation process takes place more rapidly in solution, which, originally yellow turns brownish in color with increasing age. The most important oxidation product is arsenoxide, which is many times more toxic than arsphenamine and great care must be taken to avoid the administration of solutions which have been standing more than four hours.

Neoarsphenamine is, as may be seen from its formula, a formaldehyde sulfoxylate derivative of arsphenamine base. It is an orange yellow powder containing according to formula, approximately 32 per cent arsenic. The process of manufacture, however yields a product which contains from 19–22 per cent arsenic, which is of course not chemically pure and which because of its instability cannot be purified (Harrison) It is readily soluble in water A freshly prepared solution is clear yellow in color is neutral to litmus and may be administered without alkalinization or other special procedures. Both powdered drug and solution oxidize very rapidly on exposure to air and are greatly increased in toxicity thereby This phenomenon takes place much more rapidly than with arsphenamine. It necessitates, as with the older drug marketing in vacuum or in nitrogen filled ampules it prohibits aeration of the solution (by shaking or squirting with a syringe) and it makes essential the immediate administration of the drug after preparation. The solution must not be allowed to stand exposed to air for longer than 4 hours.

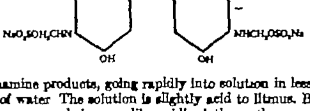


Silver arsphenamine was developed by Kolle Ehrlich s successor at the Georg Speyer Haus in Frankfort. t is supposedly a chemical compound of silver with the arsphenamine radical and is marketed as the sodium salt. Its exact structural formula is unknown, but it is thought to be approximately as indicated though Raiziss and Gavron feel it is an intimate mixture of arsphenamine and colloidal silver rather than a chemically homogeneous substance It is an amorphous brownish gray powder which contains approximately 19 per cent arsenic and 12.5 per cent silver It is readily soluble in water without shaking, and



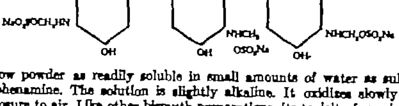
forms an almost black solution which is slightly alkaline to litmus. It may be administered without further preparation. Like other arsphenamine preparations, it oxidizes readily on exposure to air with marked increase in toxicity. Oxidation takes place more rapidly than with arsphenamine, but more slowly than with neoarsphenamine, and solutions may be allowed to stand as long as 20 minutes before use.

Sulpharsphenamine is a complex derivative of neoarsphenamine, containing two formaldehyde bisulfite groups combined with the amino radical. This product is a light yellow powder containing from 18.5–19.5 per cent of arsenic. It is more readily soluble in water than any other of



the arsphenamine products, going rapidly into solution in less than twice its volume of water. The solution is slightly acid to litmus. Both powder and solution are much less readily oxidized than other arsphenamines and remain stable for at least 24 hours. It also differs from other arsphenamines in one other important respect, i.e. it is much less irritating to tissues. This fact and its ready solubility make it suitable for intramuscular or subcutaneous injection, whereas other arsphenamines must be given by the intravenous route. Furthermore, probably because of slow absorption, sulpharsphenamine is only about one-half as toxic for animals by intramuscular or subcutaneous routes as when given intravenously.

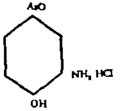
Bismarsen, a compound prepared by Raiziss, is one in which a bismuth molecule is introduced into the arsphenamine radical, perhaps in accordance with the formula suggested by Raiziss. The drug is a brownish



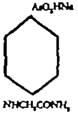
yellow powder as readily soluble in small amounts of water as sulpharsphenamine. The solution is slightly alkaline. It oxidizes slowly on exposure to air. Like other bismuth preparations, its toxicity for animals is enormously increased when it is given intravenously. This fact renders its intramuscular use imperative.

Mapharsen is the name given to meta-amino parahydroxyphenylarsine oxide by Tatum and Cooper who introduced it into the treatment of syphilis.

It is the arsenoxide of arsphenamine and was first discovered by Ehrlich who discarded it because of its supposed toxicity It is a pure chemical obtainable in crystalline form and contains 29 01 per cent metallic arsenic. It is readily soluble in water and in acid and alkali solutions. In solution it is slightly acid to methylene red but alkaline to congo red. It oxidizes slowly and upon oxidation becomes less toxic as well as less efficient therapeutically It is injected intravenously and is supplied in ampules containing also anhydrous sodium car bonate and purified sucrose.

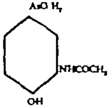


Tryparsamide the sodium salt of N phenyl-glycineamide p-arsonic acid synthesized by Jacobs and Heidelberger differs radically from all the arsphenamine compounds in that the arsenic is in penta valent rather than in trivalent form It has been studied biologically by Brown and Pearce. The drug is a white crystalline substance readily soluble in water the solution being neutral to litmus. It is perfectly stable, and is not oxidized by exposure to air It is of extremely low toxicity for animals either by intravenous or intramuscular routes. In spite of its relatively low treponemicidal activity as compared with the arsphenamines it has been found to be of value in neurosyphilis, though not in other types of syphilitic infection



This completes the roster of arsenical drugs in daily use in this country for the treatment of syphilis Two other preparations deserve brief mention *Neosilverarsphenamine* has been used to some extent in Germany, but at present is not prepared for commercial distribution by American manufacturers It is said to be more stable than neoarsphenamine and to be less productive of reactions but in our own experience (limited to about 200 injections) immediate disagreeable reactions have been frequent. This drug is to be regarded as in the experimental stage and should not be employed by the practitioner until more definite data concerning it are available

Stovarsol (also known in this country as acetarsone and in Germany as spirocide) the monosodium salt of 3-acetamino-4 hydroxyphenylarsonic acid prepared by Fourneau, and studied by Levaditi and his collaborators is an extremely interesting pentavalent arsenical drug in that unlike all other arsenicals used in the treatment of syphilis, it may be administered by mouth. The toxic oral dose in rabbits has been variously computed to range from 1000 mgm/kg (Raiziss) in a single dose to 360 mgm/kg in broken doses. This suggests marked differences in the properties of different preparations or in different batches of the same preparation. Nevertheless it has been advised for the treatment of human syphilis. The results obtained are however distinctly poorer than with the arsphenamines.



In this country it has been used largely in the treatment of amebic

dysentery and hardly at all for syphilis. Some recent reports are available of its use in the treatment of congenital syphilis. These will be mentioned in more detail in Chapter XXVII In adults, the Robinsons have shown (in 32 cases) that acetarsone by mouth is therapeutically ineffective and productive of such a high incidence of serious toxic reactions (37 5 per cent) as to render its use completely inadvisable.

The toxicity and the treponemicidal and trypanocidal activity of the commonly used arsenical drugs —The data regarding the toxicity and therapeutic efficiency of the arsenical drugs which have been described are summarized in Table 10 This information is gathered from

TABLE 10

TOXIC AND CURATIVE DOSES OF VARIOUS COMMONLY USED ARSENICAL DRUGS

Drug	Rabbit syphilis			Trypanosome infections (Mouse or rat)		
	Tolerated dose mg/kg	*Curative dose mg/kg	Therapeutic index	Tolerated dose mg/kg	Curative dose mg/kg	Therapeutic index
Arsphenamine	100–200	10–15	1 7 to 1 12	100–140	3–8	1 12 to 1 40
Neoarsphenamine	225–350	20–40	1:5 to 1 17	200–375	4–10	1 20 to 1 90
Silver arsphenamine	100–115	4–10	1 10 to 1 25	130–170	2–11	1 11 to 1 80
Mapharsen	10–14	ND†	1 4 to 1 5 6	15–20	0 8	1 23 to 1 25
Sulpharsphenamine	275–400	10–22	1 10 to 1 20	310–320	16–32	1 10 to 1 20
Bismarsen	200 (?) (I M)	20	1 15	300 (I M)	15	1 20
Tryparsamide	750–900	400	1 2	1000–2500	300	1 3 to 1 8

* Unfortunately since the interval between treatment and node transfer was in the majority of studies less than 6 months, this information is not entirely accurate.
† Not determined. 2.5 mgm/kg according to Gruhzit 12 mgm/kg according to Raiziss.

various sources including Weiss Kolmer Kolle Brown and Pearce Voegtlin Tatum and Cooper Gruhzit, and Roth and Creswell. A number of facts of interest appear Arsphenamine, mapharsen and silver arsphenamine are the most toxic members of the series for rabbits, rats and mice sulpharsphenamine neoarsphenamine and bismarsen the least toxic The pentavalent arsenical tryparsamide, is tolerated by animals in relatively enormous dosage. These results are only indirectly translatable to

human beings Certain frequent and serious complications of arsphenamine therapy in man, exfoliative dermatitis and toxic jaundice do not occur in experimental animals and the major reaction to tryparsamide in human beings, damage to the optic nerve is not observed in animals. It is important to note also that the toxicity of arsphenamine, mapharsen, and silver arsphenamine varies within narrow limits, while that of others of the arsphenamine series, particularly neoarsphenamine and sulpharsphenamine may vary as much as 100 per cent. This is due to the relative chemical instability of these two drugs lots from different manufacturers, or even different lots from the same manufacturer, varying widely both in *toxicity and therapeutic efficiency*

The tissue changes produced by toxic doses of the arsphenamines in experimental animals —Additional and equally valuable information as to the toxic effects of these drugs is available from histologic studies of experimental animals carried out by Kolmer and Lucke by Myers, and by Brown and Pearce The former studied the effects of acid arsphenamine (never used clinically) of single large doses as well as multiple small doses of properly alkalinized arsphenamine solution and of neoarsphenamine. With acid arsphenamine death was almost immediate, and there was intense generalized engorgement and thrombosis of vessels of brain and meninges, heart lungs liver spleen, kidney and suprarenal with occasional small capillary hemorrhages. With single large doses either of arsphenamine or neoarsphenamine corresponding to a 6 gram dose of the former and a 12 gram dose of the latter for a 60 kg. man, the animals (rats) survived for 2–12 days. In each group there were focal necroses in the liver extensive tubular necrosis of the kidneys with calcium deposition, and areas of focal necrosis in spleen and myocardium. Depletion of the lipoid and chromaffin content of the suprarenals was constantly present. There were occasional small focal hemorrhages in various organs With multiple injections (6–17) at intervals and in a dosage approximating those used in man tissue changes were inconspicuous with either drug, perhaps less with neoarsphenamine than with arsphenamine They consisted of occasional small areas of focal necrosis in heart muscle and liver occasional thrombosis of small vessels in viscera, slight changes in lipoid and chromaffin substance of the suprarenals and very slight connective tissue proliferation in lung liver spleen, and kidney These alterations were never such as to interfere with the function of the various organs Like tissue changes were produced by sulpharsphenamine according to Kolmer and the effect of toxic doses of tryparsamide was found by Brown and Pearce to be similar

Myers found that tissue alterations after the repeated injections of therapeutic doses of silver arsphenamine were, except for the deposit of silver granules in cells of liver bone marrow spleen and kidney, inconspicuous and, he believes negligible.

Using bismarsen in therapeutic doses (6–18 injections) Kolmer found no important tissue changes in the organs of rat, guinea pig, or rabbit *Large single doses* corresponding to 2.0 grams per 60 kg (repeated for

10–15 injections) caused tubular necrosis of the kidney and focal necrosis in the liver similar to the lesions caused by arsphenamine

Similar detailed studies for mapharsen are not yet available.

The local effect of all these preparations, when injected intramuscularly, is edema, necrosis of the muscle fibres, and leucocytic infiltration, followed by replacement with fibrous tissue. Arsphenamine produces the severest lesions when given intramuscularly, then neoarsphenamine, sulpharsphenamine, and bismarsen, in order of decreasing intensity

It must be emphasized that the dosage of any of these arsenical drugs necessary to produce generalized tissue changes such as described is many times that ever employed in the treatment of human beings and that with repeated administration of doses analogous to those employed in human therapy pathologic alterations are either conspicuous by their absence or almost entirely negligible.

Treponemicidal activity in rabbits —The curative dose in experimental rabbit syphilis is based, in most instances, on the single dose necessary to sterilize a recently infected animal completely as judged by disappearance of treponemes, healing of lesions, and the negative results of subsequent lymph node transfers to normal animals. This too is not directly translatable to human beings.

To approximate it closely it would be necessary to treat a man weighing 60 kg. with, for example, a single dose of 1 gram of arsphenamine or 2.4 grams of neoarsphenamine doses which clinical experience has shown are too toxic for use. Furthermore clinical experience has shown that human syphilis is considerably more difficult to cure than rabbit syphilis, and that this cannot be accomplished uniformly by a single dose of any drug so far discovered.

As with toxicity, the limits of variation of therapeutic efficiency (as measured by the therapeutic index) are less with arsphenamine and mapharsen than with any other members of the group Various workers in all parts of the world have found the therapeutic efficiency of the former to vary only between 10 and 15 mgm/kg and when important factors such as duration of infection in the animals are comparably controlled, to be fixed pretty closely to 12 mgm/kg. With other arsphenamine preparations, studied by different observers there may be as much as 100 per cent variability in the sterilizing doses that for neoarsphenamine varying, for example between 20 and 40 mgm/kg, depending on the product employed. As for bismarsen, there are as yet too few experimental studies available to permit conclusions as to this point. The two factors of stability in toxicity and in therapeutic efficiency are strong arguments in favor of the use of arsphenamine in the treatment of certain types of syphilitic infection.

It will be noted also that the best therapeutic indices for arsphenamine and mapharsen i.e. 1–12, 1–6.6, are less than the best reported for any other members of the series, which vary from 1–15 for bismarsen to 1–25 for neoarsphenamine. This fact, seemingly indicative of the superiority of the other drugs over old arsphenamine is again not directly translatable

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1 275,000 neoarsphenamine in a concentration of 1 1,075 000 and silver arsphenamine in a concentration of 1 825 000 Because of the limitations of the experiments, i.e., slow spontaneous death of the treponemes in the control tubes, the results of prolonged incubation of the organisms with the drugs cannot be accurately determined. The above figures, therefore probably do not represent the minimum concentration in which mapharsen and the arsphenamines are treponemicidal *in vitro* Nevertheless the values which Eagle has determined as effective in the test tube represent dilutions several times higher than those encountered in the body fluids following a single average dose of these preparations i.e a dose of 0 4 gram of arsphenamine or 0 05 gram of mapharsen to a man of 70 kilograms assuming 40 kilograms of body weight to be water and assuming uniform distribution would represent a final concentration in the body fluids of 1 100 000 and 1 800 000 respectively

It will be noted that Table 11 contains no mention of the treponemicidal activity of sulpharsphenamine. In his early experiments Eagle found that in contrast to its therapeutic activity *in vivo* (Table 10) it was 50 times less active *in vitro* than neoarsphenamine. This, he believes, is probably related to the fact that, in contrast to the other arsphenamines sulpharsphenamine *in vitro* is not readily oxidized by molecular oxygen to its corresponding arsenoxide.

Trypanocidal activity —All the drugs under consideration are more efficient in trypanosome infections of rats and mice (*T equiperdum* or *T brucei*) than in rabbit syphilis. The same relative variations in toxicity less with arsphenamine and mapharsen than with other drugs are observed. There is, however even greater variation in therapeutic efficiency depending largely on the method of study employed. In general it is true that a preparation with a high therapeutic index in experimental trypanosomiasis will also have a high treponemicidal value, but the comparison is only a rough one The lack of parallelism in the two tests is well shown by tryparsamide which has a high trypanocidal but very low treponemicidal value Trypanocidal tests cannot serve as a substitute for experimental rabbit syphilis in the study of a new drug they may be used, however to control the continued therapeutic efficiency of new lots of manufacture of a drug after treponemicidal tests have determined its probable worth.

The route of administration as influencing toxicity and therapeutic efficiency —The idea that the therapeutic value of the arsphenamines might be enhanced their toxicity reduced and the technique of treatment simplified, if they were administered by the intramuscular instead of the intravenous route is an old one dating back to Ehrlich and has been frequently revived. As a matter of fact, the first injections of arsphenamine were given intramuscularly the method being almost wholly abandoned because of severe pain and necrosis with sometimes subsequent sloughing of the buttock or lumbar muscles Neoarsphenamine and silver arsphenamine are subject to the same objection from the standpoint of pain though the danger of necrosis is less. Sulpharsphenamine and bismarsen are both capable of intramuscular injection because of

TABLE 12

COMPARISON OF TOXICITY AND THERAPEUTIC EFFICIENCY OF VARIOUS ARSENICALS BY INTRAMUSCULAR AND INTRAVENOUS ROUTES OF ADMINISTRATION

	Intravenous administration			Intramuscular or subcutaneous administration			Must be administered to human beings
	Maximal tolerated dose mg/kg	Minimal effective dose mg/kg.	Therapeutic ratio approximate	Maximal tolerated dose mg/kg.	Minimal effective dose mg/kg.	Therapeutic ratio	
Arsphenamine	100–170	12	1 10	150	11	1 14	Intravenously
Neoarsphenamine	225–350	25	1 12	130–200	14	1 15	Intravenously
Mapharsen	10–14	2 5	1 5 5	22	No data		Intravenously
Sulpharsphenamine	300–400	10–20	1 20	500–700	28	1 25	Intramuscularly
Bismarsen	30–40	15	1 2	300	20	1 15	Intramuscularly

their lower irritating properties and indeed both must be used by this route, because of enhanced toxicity when given intravenously It is of interest to compare toxicity and therapeutic efficiency of these four drugs by the two routes of administration as is done in Table 12 With all except neoarsphenamine, toxicity is lower by the intramuscular than by the intravenous route though, curiously enough, neoarsphenamine is almost twice as toxic for lower animals when given intramuscularly The effective dose of arsphenamine in experimental rabbit syphilis is about the same by either route that of neoarsphenamine is improved by intramuscular injection though, with the enhanced toxicity the therapeutic ratio remains about the same. Since these two drugs cause so much pain when given intramuscularly to human beings, and since animal experiments show no striking advantage for this method of injection it should never be employed in human beings these drugs must be given intravenously

On the other hand sulpharsphenamine is twice as toxic and bismarsen ten times as toxic, by intravenous as compared with intramuscular routes. As for therapeutic efficiency it is slightly higher for both drugs by the intramuscular route. These facts combined with the known increased incidence of serious reactions in man from the intravenous injection of sulpharsphenamine show definitely that neither of these drugs should be given intravenously they must be given intramuscularly

Data concerning the therapeutic efficiency of mapharsen administered intramuscularly to experimental animals are lacking. The local reaction following its administration by this route is similar to those produced by the arsphenamines but much less severe. Although a small number of patients with early congenital syphilis have apparently been successfully treated (Cornell and Astrachan) with mapharsen intramuscularly and while there are scattered instances of its intramuscular use in adults without untoward local reactions, its intravenous administration is the method of choice.*

The dosage of arsenicals and the margin of safety in man — The average therapeutic dose of the various arsenical drugs was at first empirically set at a level sufficiently below the maximum tolerated dose in experimental animals to be sure of complete safety for the patient. The accumulated experience of toxic effects in patients gained by the administration of many millions of injections has revised the original estimates slightly In Table 13 is shown the metallic content of the various preparations the tolerated dose in experimental animals in mgm/kg, the average maximum therapeutic dose customary in man, and, assuming that toxicity for man is approximately the same as for lower animals, the ratio of therapeutic to toxic dose for a 60 kilo human being. For all arsphenamine preparations except bismarsen this varies between 1 20 and 1 30 that is the probable minimal lethal dose is 20 to 30 times greater than the average therapeutic dose.

The ratio of 1 10 for mapharsen is the lowest of all the arsenical

* Solu-salvarsan (sodium 3 4 diacetyl-amino-4 hydroxy-arsenobenzene 2' sodium glycolate) is a new German preparation which can be given intramuscularly However it is so toxic that its use has been abandoned.

TABLE 13

THE MARGIN OF SAFETY OF ARSENICAL PREPARATIONS USED IN THE TREATMENT OF SYPHILIS IN MAN

	Arsenic content, per cent	Silver content, per cent	Bismuth content, per cent	Maximum tolerated dose, gm/kg.	Average maximum therapeutic dose, gm. 60 kg man	Ratio of therapeutic to toxic dose
Arsphenamine	31			0 140	0 4	1 21
Neoarsphenamine	19			0 375	0 9	1:25
Silver arsphenamine	19	12 5		0 170	0 3	1 34
Mapharsen	29			0 010	0 06	1 10
Sulpharsphenamine	18 5–19 5			0 320	0 6	1 30
Tryparsamide	25			0 620	3 0	1 12
Bismarsen	12–15		23–25	0 300	0 2	1 90

preparations used in the treatment of syphilis. There is some evidence however that this drug can be given safely in larger doses than those commonly employed at the present time perhaps because of its relatively rapid excretion (cf p 20) The low therapeutic ratio of mapharsen is compensated for somewhat by the ability to administer it in the recommended dosage at three day (or even shorter) intervals with comparative safety

For bismarsen the ratio of therapeutic to toxic dose is 1 90 but the small dose necessary to avoid reactions in human therapy is compensated for by the fact that injections may be given at more frequent intervals than with other products For tryparsamide the ratio is 1 12 but this is permissible since the administration of this drug is singularly free from generalized unpleasant after effects. The margin of safety in antisyphilitic treatment is therefore wide

Comparisons of maximum tolerated (MTD) and minimum lethal (MLD) doses of the several trivalent arsenical products potentially so important in the massive dose treatment of early syphilis (see Chapter XXXIII) are difficult accurately to define and except for arsphenamine, *neoarsphenamine and sulpharsphenamine (Table 14)* are largely lacking from the literature From the data of Table 14 however it appears likely that MTD is roughly 60–80 per cent of MLD i e the margin of safety is a very narrow one

Pharmacology of the arsphenamines —It is essential for the practitioner to be familiar with the known important fact as to the fate of the arsphenamine products administered to human beings and the

TABLE 14

THE RELATIONSHIP OF MAXIMUM TOLERATED TO MINIMUM LETHAL DOSE OF CERTAIN ARSENICAL DRUGS IN ANIMALS (WEISS)

Compound	Maximum tolerated dose mgm/kg (MTD)	Minimum lethal dose mgm/kg (MLD)
Arsphenamine	200 (rabbits) 175 (mice)	100 (rabbits) 170 (mice)
Neoarsphenamine	500 (mice)	870 (mice)
Sulpharsphenamine	320–480 (rats)	210–320 (rats)

physiologic effects which they may exert. Chemical analyses of blood and tissues of experimental animals have shown that when any of these products are injected intravenously they begin to disappear from the blood stream within a few minutes of injection and that after 3–4 hours they are present in the circulating blood only in minute traces. The rate of disappearance and the actual concentration in the blood are of practical importance in the therapeutic procedure of the intraspinal or intracisternal administration of arsphenaminized serum in the treatment of neurosyphilis. Fordyce and his associates conducted an elaborate series of studies on this point, with results which are confirmatory of the studies of others.

The elimination of the arsphenamines, tryparsamide and mapharsen from the body takes place largely by way of urine and feces, approximately 50–90 per cent of these drugs being excreted by these routes within one week. This is the factor responsible for the customary interval of one week between injections. The substances excreted are both inorganic and organic compounds, the latter largely aminophenols. The remainder is apparently stored in the tissues and slowly excreted over a long period of many weeks. In the urine, arsenic appears within an hour or two of injection of any of the arsphenamines from 8–18 per cent of the arsenic administered is excreted within the first 3 days thereafter in amounts decreasing to a trace for as long as 14 days. Arsenic appears in the bile within a few minutes of injection, and, in the case of arsphenamine, more than half of the total excretion appears in the feces within the first week. Elimination varies slightly with different products thus the major part of the excretion of arsphenamine occurs in the feces that of neoarsphenamine and mapharsen in the urine. With serial injections at weekly intervals, excretion is increased by both routes there is definite evidence of storage in the tissues and all of the drug may not be eliminated for weeks after the last injection. Small quantities may be excreted in sweat, saliva, and milk, the latter a point of possible importance in the treatment of nursing infants with congenital syphilis.

Chemical analysis of tissues shows that as the arsenic disappears from the blood stream, it is promptly taken up and presumably stored by the liver lungs, and kidneys Appreciable amounts may also be found in the skin. By far the largest part is retained in the liver or as in the case of mapharsen in the spleen. Whether it is taken up again from these organs by the blood stream for subsequent distribution to the tissues as un-

changed arsphenamine or as arsenoxide is not clear The work of Rosenthal indicates that the arsphenamines are changed in the tissues to arsenoxide before they re-enter the blood stream. At any rate they appear to retain therapeutic activity for the several days of maximum excretion immediately following injection perhaps for 3–7 days. Later than this, ingenious experiments indicate that the residue of stored arsenic has lost its therapeutic activity That it may still be capable of exerting toxic effects is suggested by the *relatively high incidence (in human beings)* of post-arsphenamine reactions involving such storage areas as liver and skin (jaundice and dermatitis)

The penetrability of the arsphenamines into the nervous system —In view of the great frequency of central nervous system involvement in syphilis many investigators have attempted to determine the relative penetrability of the various arsphenamines and of tryparsamide into the nervous system These studies have been conducted along three lines determinations of arsenic content of brain, spinal cord and cerebrospinal fluid of experimental animals similar studies of the cerebrospinal fluid of treated human beings and biologic tests of the curability of various products on trypanosome or spirochetal infections produced in animals by the intradural inoculation of organisms. The results obtained by these methods are conflicting and difficult of interpretation. After the injection of any of the arsphenamines arsenic is present in only small quantities in nervous tissues or cerebrospinal fluid of animals or man, but may be found in these areas in about 80 per cent of treated patients Cornwall and his associates summarize these latter investigations as follows in Table 15 From these data, one would be justified in concluding that silver arsphenamine was of more value than other arsphenamine products or tryparsamide in the treatment of neurosyphilis.

TABLE 15

ARSENIC IN THE SPINAL FLUID (AFTER CORNWALL, BUNKER AND MYERS, AND FORDYCE, ROSEN AND MYERS)

Drug	Per cent of patients showing arsenic in cerebrospinal fluid	Average amount of arsenic present, in mgm. per 100 gm of cerebrospinal fluid
Arsphenamine	77.5	4
Neoarsphenamine	77	5–10
Silver arsphenamine	70–85	11 5–12 5
Tryparsamide	100	2 2 5
Mapharsen	No determinations	

In contrast to the findings of Cornwall, Hawking and his associates were able to demonstrate only minute amounts of arsenic in the spinal

fluid following the administration of silver arsphenamine. Employing the biologic method used by Voegtlin and his associates and by Raiziss and Severac Hawking found in agreement with these observers, that the great difference between tryparsamide and the trivalent arsenicals lies not in the total amount of arsenic which enters the spinal fluid but in "the appearance therein *of trypanocidally active arsenic, i.e. arsenic in a* form capable of penetrating the nervous system and sterilizing animals infected with trypanosomes introduced into the subarachnoid space. This is in agreement with the clinical observation that the drug which appears in the cerebrospinal fluid and brain tissue in highest concentrations is not necessarily the best for the treatment of neurosyphilis in man. Tatum (personal communication) has aptly summarized the situation by pointing out that "The final proof of efficiency of an antisyphilitic drug is not where it is but what it does' At present, therefore there is no clear-cut experimental evidence available suggesting the advisability of the use of any particular arsphenamine product in neurosyphilis one must depend largely on clinical impressions.

Assuming that it is desirable to increase the concentration of arsenic in the cerebrospinal fluid in the treatment of neurosyphilis this may be accomplished by any one of a variety of methods, calculated to alter the permeability of the meningeal-choroid plexus barrier between blood and cerebrospinal fluid. This factor to be discussed in more detail in the chapter on the treatment of neurosyphilis, may be influenced by such diverse procedures as spinal drainage, the subdural injection of various irritants the intravenous *injection of hypertonic saline solutions jugular compression*, or fever The use of any one of these in combination with, or immediately followed by the intravenous injection of an arsphenamine materially promotes the penetration of the latter into nerve tissues and cerebrospinal fluid

Raiziss and Severac suggest the interesting possibility that because of their greater penetrating power pentavalent arsenicals will be found to be more suitable for the treatment of neurosyphilis than the trivalent arsphenamines. Trivalent compounds tend to form colloidal precipitates when added to serum, and presumably may form similar colloidal precipitates in tissue fluids. They are, therefore, not as capable of penetrating animal membranes as the pentavalent drugs. This fits in with the known value of tryparsamide in the clinical treatment of neurosyphilis.

The effects of the arsenical drugs on blood pressure kidneys blood heart, and liver —Given in average therapeutic doses to individuals in good general physical condition and barring reactions, the arsphenamines have no appreciable effect on blood pressure, on kidney function as measured by phthalein output or blood chemistry on the cellular elements or the coagulation time of the blood or on the electrocardiogram. With certain toxic reactions, alterations in one or several of these respects may occur *These will be discussed in their proper place.* There may be a slight transitory albuminuria, usually without cylindruria, for a day or two following injection but this is not accompanied by any measurable change in kidney function. All the arsenical preparations are

mildly stimulating to erythropoiesis as is most easily seen in patients with mild secondary anemia.

The effect of therapeutic doses of the arsphenamines on the liver has been studied by means of various tests for liver function chiefly dye retention tests (for example bromsulphalein) and the estimation of bile pigments (bilirubin) in the blood. There is some evidence of slight liver damage in about 25 per cent of patients under treatment though rarely is this extensive enough to produce symptoms of intoxication (see section on post-arsphenamine jaundice in Chapter VII)

Measurements of the efficiency of arsenical drugs in man — Several of the criteria which determine the worth of an arsenical preparation in human syphilis should be further mentioned here These are (1) the disappearance of surface treponemes from the moist lesions of primary and secondary syphilis (2) the rapidity of healing of visible lesions and (3) the immediate effect on the blood serologic test in patients with early syphilis. These three criteria are valuable in the same sense as the relatively rough indices of therapeutic testing in animals They provide some information of worth but not enough to determine the final status of the drug in syphilotherapy which, in the last analysis can only be judged by its success or failure in curing syphilis Discussion of the question of cure must await detailed consideration in subsequent chapters dealing with various types of syphilitic infection

The disappearance of surface treponemes —The administration of therapeutic doses of any of the arsphenamine products is followed by disappearance of surface treponemes from the moist lesions of early syphilis, as determined by repeated darkfield examinations within 12-24 hours Bismarsen is the only exception to this statement with this drug from 75-150 hours are required Curiously enough, during the first 1-4 hours after the injection of any of these drugs there is often a definite *increase* in the number of treponemes present in the serum expressed from lesions as has been shown both by Frei and Leipold. Arsphenamine is according to Leipold the most effective product in causing prompt disappearance of organisms after an intravenous injection of 0.3-0 4 gram they have gone in 4 to 6 hours Mapharsen in a dosage of 0 060 gm. is equally effective The rate of disappearance is proportionate to the dosage, as Leipold has shown with silver arsphenamine, i.e.

Dosage	*Time of disappearance of surface treponemes*
0 1 gm.	20-56 hours
0 15 gm.	27-32 hours
0.2 gm.	17-25 hours
0.25 gm	6-7 hours
0.3 gm.	5-7 hours

With small doses (0 1 gm arsphenamine or silver arsphenamine 0.2-0 45 gm. neoarsphenamine 0 010 gm. mapharsen) surface organisms may not

be destroyed at all.* In order, the effectiveness of the arsenicals in this respect appears to be arsphenamine, mapharsen silver arsphenamine sulpharsphenamine, neoarsphenamine and bismarsen. Tryparsamide as might be expected from its comparatively slight treponemicidal activity in experimental animals will not cause the disappearance of treponemes from surface lesions in double the average therapeutic dose, and is of no value in the treatment of early syphilis

The effect on healing of lesions —Almost without exception visible lesions of syphilis (on skin or mucosae) heal promptly after the administration of any of the arsphenamine products Healing is much more rapid than with any bismuth or mercurial preparation. Comparative data as to the rate of disappearance of active lesions in comparable series of patients treated with different preparations under identical conditions of control, are not available except as between arsphenamine and neoarsphenamine. Cannon and Karelitz, in a careful study limited to patients with early syphilis have estimated the average dose the average number of injections, and the average number of days necessary for the healing of visible lesions in a fairly large series of patients Their data, compressed for simplicity are shown in Table 16 To this table have been added similar data concerning mapharsen compiled from the reports of Foerster

TABLE 16

COMPARATIVE EFFECT OF ARSPHENAMINE, NEOARSPHENAMINE AND MAPHARSEN IN EARLY SYPHILIS (AFTER CANNON FOERSTER ET AL., COLE ET AL.)

Average Treatment and Time Necessary for Disappearance of Visible Lesions

	Cases	Average total dosage necessary grams	Average number of injections necessary	Average number of days
Arsphenamine	32	1 3	2 7	14
Neoarsphenamine	61	3 8	5 8	23
Mapharsen	151	23	4 4	13 4

and his associates and Cole and his co-workers. Analyzed separately the results of these two groups of investigators are practically identical, and although they are not directly comparable to the findings of Cannon with arsphenamine and neoarsphenamine their inclusion is justified. All groups contain approximately one-third patients with primary syphilis (seronegative or seropositive) and two-thirds patients with secondary

However attempts to increase therapeutic efficiency by the administration of large doses of arsphenamine at short intervals (e.g 0 6 gm. arsphenamine every day for 3–4 days, Pollitzer) do not succeed. The test of clinical use (Chapter XIII) shows that this method produces ultimate results as poor as haphazard irregular treatment.

The new technique of administering arsenicals by massive continuous intravenous drip will be discussed later (Chapter XXXIII)

syphilis. The average dosage of neoarsphenamine necessary to produce healing was almost three times as great (even in terms of arsenic equivalent dosage, almost twice as much) the number of injections twice as many and the number of days 50 per cent greater than that of arsphenamine. While mapharsen is not as effective as arsphenamine it is appreciably better than neoarsphenamine

From such scattered data as are available in the literature and from personal experience, we should rank the various products in this respect as follows arsphenamine, mapharsen, silver arsphenamine, sulpharsphenamine neoarsphenamine, bismarsen. Tryparsamide has practically no effect on the healing of lesions in early syphilis in double the average therapeutic dose

The effect on the serologic test —Here again there are available almost no data of value except for arsphenamine and neoarsphenamine for a comparison of the effect of the various arsphenamines in reducing a positive serologic test to negative For a satisfactory comparison all patients must be treated while in the seropositive primary or early secondary stages, since later than this the serologic response is so variable from any form of treatment as to make the results valueless a large series of patients must be studied and the serologic technique used must be approximately the same throughout the experiment. The sensitivity of the complement fixation varies so much with the antigen employed or with the type of preliminary incubation (water bath or icebox) and the sensitivity of flocculation tests with the particular technique chosen that it is almost impossible to compare results as between two different clinics. Four studies are available, however each of which is largely confirmatory of the other

In addition to observing the comparative effect of arsphenamine and neoarsphenamine on the healing of lesions Cannon has provided valuable data as to the average dose of each drug, the average number of injections and the average number of days necessary to reduce the positive blood Wassermann to negative in a large series of patients with seropositive primary or early secondary syphilis (eliminating of course, seronegative primary syphilis since here the Wassermann was negative before treatment) These figures, again compressed from Cannon s paper for simplicity are shown in Table 17 The same superiority for arsphenamine over *neoarsphenamine is apparent as in respect of healing of lesions*

More recently Cannon has compared the effects of silver arsphenamine (in 104 patients) with those of arsphenamine and neoarsphenamine in early syphilis. As regards the average number of doses and the time necessary to heal lesions and to reverse the Wassermann, arsphenamine ranks first, silver arsphenamine second, and neoarsphenamine a poor third. Unfortunately the comparison is not strictly accurate since all the patients receiving silver arsphenamine were also given simultaneous intramuscular injections of insoluble mercury or bismuth salts while this form of combined treatment was not carried out as a routine in the earlier reported arsphenamine and neoarsphenamine series, from which the contrast is drawn. Authoritative data permitting the ranking of silver arsphenamine in respect to ultimate clinical outcome in early syphilis are as yet lacking.

TABLE 17

COMPARATIVE EFFECT OF ARSPHENAMINE AND NEOARSPHENAMINE IN EARLY SYPHILIS (AFTER CANNON)

Average Treatment and Time Necessary for Reversal of Blood Wassermann to Negative.

	Cases	Average total dosage, grams	Average number of injections	Average number of days
Arsphenamine	103	3.9	9.7	75
Neoarsphenamine	110	7.1	13.4	99

Another method of approach to the problem is shown in Table 18 where are presented data showing the effect of a single course of treatment on the blood Wassermann of patients with early syphilis (seropositive primary and early secondary) The table is based on patients in the Johns Hopkins Hospital prior to 1926 the first course of treatment consisting either of 6 or 8 weekly injections of arsphenamine *without* simultaneous mercury or bismuth therapy and using a Wassermann system with a 0.2 per cent cholesterolized antigen and one-half hour preliminary incubation in the water bath (a relatively insensitive Wassermann test as compared with that used by Harrison) Compared with this are patients treated at St. Thomas' Hospital by Harrison, the first course of treatment consisting of 10 injections of neoarsphenamine, simultaneously with either mercury

TABLE 18

COMPARATIVE EFFECT OF ONE COURSE OF ARSPHENAMINE OR NEOARSPHENAMINE ON THE BLOOD WASSERMANN IN EARLY SYPHILIS

		Cases of seropositive primary or early secondary syphilis	Per cent with blood Wassermann at end of first course		
			Negative	Incompletely positive	Positive
Moore and Kemp Arsphenamine no mercury or bismuth	6 injections (1.8–2.4 gms.)	424	68.6	17.2	14.0
	8 injections (2.4–3.2 gms.)	227	81.5	7.4	10.5
Harrison Neoarsphenamine plus mercury or bismuth	10 injections (6.3 gms.) + average of 7 gms. mercury	120	74.4	13.9	11.6
	10 injections (6.3 gms.) + average of 3.6 gms. bismuth	114	74.5	20.1	5.4

or bismuth in addition, and using a Wassermann system considerably more delicate than that employed with our own patients. The comparison is not a fair one because of the complicating factor of mercury or bismuth therapy in addition to neoarsphenamine and because of the difference in sensitivity of the two Wassermann techniques. Taking both these factors into consideration however it seems probable that the effect of 8 injections of arsphenamine alone is capable of accomplishing about as much toward reversal of the Wassermann as 10 injections of neoarsphenamine (with twice as great a total dosage) plus a heavy metal With either sys-

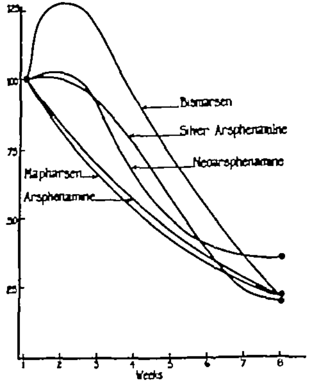


FIG. 9 —The average curves of quantitative Wassermann response for the five drugs studied are superimposed for purposes of direct comparison.

tem from 75–80 per cent of patients with early syphilis will have negative blood Wassermanns at the end of the first course of treatment.

A more accurate picture of the rôle of various arsenical preparations in causing reversal of the blood Wassermann is derived from a study by Moore and his associates. This study included only patients in the seropositive primary or secondary stage of the infection instead of the qualitative Wassermann technique employed by previous observers all tests were quantitated and were repeated at weekly intervals Their results shown in Fig. 9 are in some respects surprising. As one might expect, arsphenamine and silver arsphenamine were approximately equally

efficient in causing Wassermann reversal. Mapharsen, which had not been previously studied in this regard, was identical in behavior with those two preparations Surprisingly, bismarsen a preparation recommended only as an alternative in the treatment of early syphilis, was not only as efficient as arsphenamine and silver arsphenamine but was appreciably better than neoarsphenamine in causing serologic reversal. Since the preparations included in Fig 9 are by no means equal in therapeutic efficiency except in their effect on reversal of the serologic test in early syphilis this method for evaluating antisyphilitic drugs must be considered to be of limited value only

The mechanism of action of the arsphenamines —It was Ehrlich's opinion that the treponemicidal activity of the arsphenamines was due to their direct action on the organism. *In vitro* experiments failed to confirm this impression and later Voegtlin and Smith and Rosenthal showed that oxidation of the arsphenamines in the body to arsenoxide was necessary to elicit treponemicidal activity The subsequent (but so far incomplete) studies of Eagle have carried us a step nearer to an exact understanding of the mechanism of antisyphilitic drugs. Eagle has found that the antispirochetal action *in vitro* of arsenoxide (m-amino-p-hydroxyphenyl-arsenoxide) and bismuth compounds was unaffected by the removal of molecular oxygen [from the spirocheto-arsenical mixture] and is probably due to these compounds as such. In marked contrast, neoarsphenamine, which is highly spirocheticidal when dissolved aerobically was negligibly so when dissolved and tested under nitrogen in the absence of oxygen. Its relatively marked antispirochetal action when tested aerobically (25 to 60 times that observed under nitrogen) is apparently due to its oxidation by molecular oxygen to other directly spirocheticidal compounds This oxidation did not require the presence of tissue derivatives and proceeded so rapidly that solutions became actively spirocheticidal within 3 to 5 minutes.

"Commercial arsphenamine and silver arsphenamine were intermediate between arsenoxide and neoarsphenamine in that although two-thirds to seven-eighths of their antispirochetal activity *in vitro* was due to oxidation products there was a small but significant residual activity in the absence of oxygen. In the case of arsphenamine a large part of this residual activity was accounted for by arsenoxide or by arsenoxide-like substances present as an impurity

"Sulfhydryl compounds (cysteine glutathione and thioglycollic acid) added in sufficient excess to arsphenamines arsenoxide bismuth or mercury compounds, almost completely abolished their antispirochetal action *in vitro* The large excess which was necessary to cause complete inactivation of the arsenical suggests that the addition compound may be readily hydrolyzed. Thiamin chloride and methionine which contain a -S- rather than a -SH group had no inhibitory effect.

Eagle concludes "These findings are of interest in relation to the thesis that the antispirochetal action of arsenic, bismuth, and mercury compounds may rest on their common affinity for sulfhydryl groups in the *T pallidum* "

or bismuth in addition, and using a Wassermann system considerably more delicate than that employed with our own patients. The comparison is not a fair one because of the complicating factor of mercury or bismuth therapy in addition to neoarsphenamine and because of the difference in sensitivity of the two Wassermann techniques Taking both these factors into consideration however, it seems probable that the effect of 8 injections of arsphenamine alone is capable of accomplishing about as much toward reversal of the Wassermann as 10 injections of neoarsphenamine (with twice as great a total dosage) plus a heavy metal. With either sys-

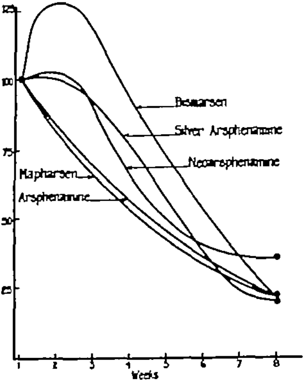


FIG. 9 —The average curves of quantitative Wassermann response for the five drugs studied are superimposed for purposes of direct comparison.

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Chapter VII

THE REACTIONS PRODUCED BY THE ARSENICAL DRUGS USED IN THE TREATMENT OF SYPHILIS

The Local Accidents from the Trivalent Arsenicals

Infiltration of the tissues.—If any of the arsphenamines (or mapharsen) except sulpharsphenamine is injected into the tissues rather than intravenously, there is immediate intense burning pain at the site of injection. The accident occurs, of course during faulty attempts at intravenous medication the patient exclaims with pain, and the operator may see a subcutaneous lump developing about the point of the needle. The injection must be interrupted at once If only a drop or two has been spilled into the tissues, the patient will have a sore aching arm for a few hours, without further difficulty If more than this there promptly develops brawny edema with redness of the overlying skin, and intense pain severe enough to cause sleepless nights and loss of function of the arm. The pain may last a week or more the swelling and disability for several weeks. With extensive infiltration of the tissues there may be central softening of the area, with a necrotic slough involving the skin and sometimes requiring months to heal There may result crippling deformities due to fibrous scars about the elbow and necessitating plastic operation. Tryparsamide* does not cause this difficulty being non-irritating to the tissues

The best treatment of this accident is its prevention by means of meticulous intravenous technique If the injection is interrupted at the first complaint of burning pain, serious trouble will be avoided If a visible lump of infiltrated arsphenamine appears, bleeding from the needle puncture wound should be promoted and the injected drug milked out if possible, by gentle pressure It has been suggested that a few cc of sterile 10 per cent sodium thiosulphate solution be injected immediately into the infiltration, or that 1 0 gm be given intravenously into the same vein but distally to the infiltration with a tourniquet applied high up on the arm. The idea of this procedure is to allow the sodium thiosulphate to diffuse into the extravasation through the first needle puncture wound by virtue of the pressure of the injection. We have tried injecting this drug directly into the infiltration but have not been convinced that we did any more than add to the patient's acute discomfort Later treatment consists in prolonged hot applications (compresses) support of the arm by a sling, sedatives for the relief of pain, and incision and drainage if fluctuation develops.

* While tryparsamide and mapharsen are not members of the arsphenamine series, their share in causing certain of the toxic complications of the arsphenamines will be briefly mentioned at appropriate points.

Pain in the arm during injection —With overalkalinized arsphenamine always with mapharsen fairly frequently with silver arsphenamine rarely and with neoarsphenamine and tryparsamide not at all, there is aching pain running up the course of the vein toward the shoulder down to the fingers or both. With arsphenamine *this is due to the excess* alkalinity of the solution it may be obviated by correct alkalinization and by the use of sterile normal salt solution as a diluent With silver arsphenamine its cause is unknown. It often presages thrombosis of the vein. With mapharsen it is due to spasm of the vein and can be prevented either by thorough aeration of the solution (by squirting it from syringe to container during mixing) in order to remove the CO_2 formed by the sodium carbonate with which mapharsen powder is mixed in the ampule by rapid injection of the drug as usually diluted or by diluting it with 25 to 50 cc of water Pain along the course of the vein occurring after or during the administration of any of the antisyphilitic drugs can usually be immediately relieved by the application of cold compresses or ice packs.

Thrombophlebitis —Again with overalkalinized arsphenamine, but not with the other arsphenamines or tryparsamide (rarely with mapharsen) thrombosis of the injected vein commonly occurs. The vein is painful, often along its whole course within several hours after injection, it is palpable as a firm tender cord, and may show a linear bruised discoloration of the overlying skin. The liability to thrombosis from arsphenamine itself is decreased by using salt solution rather than water as a diluent and by the injection of the mono- rather than the disodium salt. In certain patients a tendency to thrombosis develops even when arsphenamine is properly alkalinized, and each injection may result in this difficulty This factor is important, in that in order to save available veins for further treatment, a shift from arsphenamine to another product may be essential.

The thrombus is firmly attached to the vein wall and there is no practical danger of pulmonary embolism Among several thousand examples of venous thrombosis in our own clinics we have seen a probable pulmonary infarction only once.

There are reported instances of the thrombosis of distant veins (e.g. the vena cava iliac, femoral, etc.) after the injection of an arsphenamine into an arm vein but these are so rare that none has been observed in our clinic

The General Reactions Following the Arsphenamines

General reactions are classified in several ways most frequently perhaps on the basis of the time of their occurrence A more satisfactory classification is modified from that of Keri as follows

The Jarisch-Herxheimer reaction.

The reaction produced by acid arsphenamine

The reactions common to intravenous injections i e dependent on the route of administration rather than on the injected drug.

The angioneurotic symptom complex.

Reactions due to myocardial injury

The post-arsphenamine dermatitides

Reactions due to injury to the nervous system.
The blood dyscrasias.
Post-arsphenamine jaundice.
Renal injury from the arsphenamines.

These various complications will be separately considered.

The Jarisch-Herxheimer Reaction Therapeutic Shock

There is a close analogy between the Jarisch-Herxheimer reaction caused by the arsphenamines and mapharsen (or less frequently and with less intensity by bismuth or mercury) in syphilis and the reaction produced in tuberculous patients by the subcutaneous injection of tuberculin. When tuberculin is given in this manner to a patient with, let us say, cutaneous tuberculosis, three phenomena occur There is a general constitutional reaction of fever malaise etc. a local reaction at the point of injection of tuberculin and a focal reaction in the tuberculous lesion which, a few hours later, becomes more inflamed and edematous. Though the Herxheimer reaction does not partake of the biologic nature of the tuberculin reaction, in so far as there is no reaction at the site of injection of the drug the general and the focal reactions are both present. They are assumed to be due to the sudden destruction of large numbers of *T pallida* and the liberation and absorption of their proteins or endotoxins.

To take early syphilis as a prototype, the first injection of an arsenical drug is usually followed in a few hours by elevation of temperature to 37.9–39 4°C (100–103°F) or more (this is sometimes preceded by a chill) and by generalized aching, malaise, etc. This persists for 12–24 hours, then disappears. At the same time, cutaneous lesions of syphilis, if present, are intensified for a day or two If treatment is started in the seropositive primary stage, a profuse secondary rash may blossom out within 24 hours after the first dose. The patient with early syphilis should be warned to expect this constitutional reaction after the first, but not after subsequent injections.

The pain of bone lesions is usually greatly intensified after the first arsenical injection. Even in latent syphilis, a febrile constitutional reaction may occur In most patients it is sufficient for the the physician to know that this reaction—otherwise known as therapeutic shock—may occur It is of little practical significance. In three sets of circumstances, however the avoidance of the reaction may be of life-saving importance. These are —in gumma of the larynx in cardiovascular syphilis and in some patients with central nervous system syphilis.

If a large dose of an arsenical is given to a patient with gumma of the larynx, the edema and swelling occurring within a few hours may so impede respiration as to necessitate an emergency tracheotomy and, if this is not done to suffocate the patient. We have twice seen such an accident. In cardiovascular syphilis, the unpredictable possibility of involvement of the coronary orifices constitutes the main danger Equally dangerous is aortic aneurysm A Herxheimer reaction may cause coronary occlusion or aneurysmal rupture If there is marked cerebral vascular or cortical involvement in neurosyphilis—and this too is largely unpredict

able—the sudden edema and infiltration of the vessel wall may cause *cerebral hemorrhage or precipitate an acute paresis.* In actual practice this is less frequent than might be expected, but its possibility must be considered and guarded against

Therapeutic shock may be minimized or prevented (1) by initiating treatment with a small dose of an arsenical (0 1 gm arsphenamine 0 020 gm mapharsen 0 15 gm neoarsphenamine) or (2) by a thorough preparatory course of treatment with a heavy metal and potassium iodide With *tryparsamide, the phenomenon is much less marked than with the trivalent arsenicals* and though it may occur after bismuth or mercury it is of such slight intensity as to be negligible

The theoretical possibility of the development of a serious Herxheimer reaction in cardiovascular or central nervous systems in patients with late syphilis (whether apparently latent or with clinical manifestations involving these or other structures) has led many competent syphilotherapists *to insist that in all patients with latent or late syphilis, treatment be* initiated with a long course of heavy metal before an arsenical drug is employed. To us this seems excessive caution. In an experience of many thousand patients with various forms of late syphilis whose treatment was started with conventional doses of an arsphenamine we have seen a serious *unanticipated* Herxheimer reaction only once this in a paretic patient who suddenly developed pseudobulbar palsy within 8 hours *following an initial injection of 0 6 gm. arsphenamine. In our own practice* the initiation of treatment with a trivalent arsenical drug is scrupulously avoided in all patients with gummatous laryngitis or with clinically recognizable cardiovascular syphilis or vascular neurosyphilis of any type but in patients with other types of late syphilis we see only a theoretical rather than a practical risk in such a procedure

The Reaction Caused by Acid Arsphenamine

If acid arsphenamine (the original solution before alkalinization) is injected intravenously a series of phenomena occur with devastating rapidity An immediate sense of oppression and pain in the chest followed by intractable bursts of coughing *are usually the first symptoms. This is* rapidly followed by excruciating back pain ashen pallor syncope circulatory collapse and, if the dose has been large enough, death within a few moments Or the patient may complain of nothing during injection but, on arising from the table, drop dead as if felled by a blow If the dose exceeds 0.2 gram death is almost inevitable The mechanism of the reaction apparently depends on intravascular precipitation of the acid drug *the intravascular agglutination of erythrocytes,* and the rapid formation of multiple minute pulmonary emboli.* The rapidity of embolus formation and their multiplicity produce almost exactly the effect of a single massive pulmonary embolus.

* Shivers thinks that pulmonary embolism and subsequent bronchopneumonia may follow the intravenous injection of other arsenicals than arsphenamine if the pH of the solution is below 7 and that deterioration of the drug in the ampule may result in this excess acidity Under these circumstances, the drug is thought to precipitate in chemical combination with blood proteins.

This reaction is of course to be avoided at all cost by (1) thorough inspection of the ampule and reading of the label (2) alkalinization of arsphenamine carried out in person by or under the direct eye of the physician who is administering the injection Such accessory safeguards as adding a drop of phenolphthalein solution to verify alkalinization do not, in our experience offer more protection

If during an arsphenamine injection the patient complains of chest oppression, and coughs violently the injection should be at once interrupted until the correct alkalinization of the drug is verified. If only a small amount has been given recovery will probably occur The patient should be kept absolutely at rest for 24–48 hours circulatory collapse may be combatted by adrenalin (0 6–1 0 cc. intramuscularly or in case of great emergency, 0.2–0.3 cc. given *very slowly* intravenously) External warmth, oxygen inhalations and adrenalin should all be tried if there is time

Reactions Due in Part to the Route of Injection, in Part to the Drug

The tubing reaction —Stokes and Busman demonstrated that certain brands of gum rubber tubing (used in a gravity apparatus) contain when new a toxic agent which gradually disappears from the tubing with use, and which may be removed by soaking new tubing in 4 per cent sodium hydroxide solution for 6 hours followed by thorough rinsing. If new tubing is used without this precaution, reactions may be produced characterized by chills developing within 30–60 minutes of injection a sharp rise in temperature to 39 4°C (103°F) or over nausea, vomiting diarrhea, headache, and sweating. This usually disappears in a few hours but is followed by prostration lasting several days

The reaction is entirely preventable.

The 'ether' odor of the arsphenamines —Most patients are conscious of the odor of arsphenamine and neoarsphenamine and sometimes of mapharsen (but not of silver arsphenamine or tryparsamide, nor of products given intramuscularly such as bismarsen and sulpharsphenamine) The odor is described as resembling a mixture of ether and garlic. It appears within about 10–45 seconds after intravenous injection is started, and is an interesting physiologic demonstration of the velocity of blood flow since the odor is due to the actual passage of drug-containing blood through the capillaries of the nasal mucosa. It is caused in part by the arsenic and in part by the use of ether in the manufacture of these drugs. In some sensitive patients the odor is so intolerably disagreeable and nauseating that it raises a serious impediment to the continuation of treatment. Fortunately it may be entirely obviated by the simple expedient of having the patient hold his nose tightly between finger and thumb during the injection, breathing meanwhile through his mouth. Some patients may prefer to sniff the fumes of aromatic spirits of ammonia, or to chew gum or a mint.

Gastro intestinal reactions —Intravenous injections of various substances even including normal saline solution are prone to be followed by gastro-intestinal disturbances This is the commonest form of reaction after the arsphenamines. It appears usually 4–12 hours after treatment

and is characterised by malaise headache, nausea, vomiting, and diarrhea. Ordinarily these symptoms last a *few hours only* but *they may be prolonged* for several days.

Under ideal conditions about 40 per cent of all injections of arsphenamine 25 per cent of neoarsphenamine, and 15–20 per cent of silver arsphenamine or mapharsen will be followed by such reactions. Women are more frequently affected than men. Intramuscular *injections of bismarsen or* sulpharsphenamine are much less frequently responsible and tryparsamide, given intravenously, rarely causes this type of disturbance.

These reactions are due to a variety of causes most important of which are impurities in the distilled water employed,* under-alkalinization of arsphenamine, excessive speed of injection dietary *indiscretions or constipation* on the part of the patient. The latter factors are perhaps most largely contributory A full meal just before or just after an injection of an arsphenamine is likely to be vomited and this seems particularly true if the patient tends toward constipation. It is good advice to warn the patient to eat lightly on the day of treatment, even to omit the following meal entirely, and to regulate his bowels if necessary by means of a mild purgative taken the night before (mineral oil, a saline cathartic etc)

Many attempts have been made to decrease gastro-intestinal reactions to arsphenamine and neoarsphenamine by administering them in solutions of sodium thiosulphate glucose amino acetic acid, certain vitamins, liver extract, and sodium dehydrocholate or by the simultaneous oral administration of certain of these substances especially vitamin C We have had experience with several of these preparations and have found only one sodium dehydrocholate to be of any value. Unfortunately there is very little if any experimental evidence to show that the toxicity of the arsphenamines is actually decreased by these substances, and if it is that it is not also accompanied by a decrease in therapeutic efficiency (Doak) † In addition the use of most of them adds materially to the cost of treatment.

If reactions of this type are mild and of short duration, they may be disregarded in subsequent treatment especially in patients with early syphilis or in pregnant women. If on the other hand, the reaction is prolonged for a day or more, attempts must be made to obviate it in further treatment by reduction of dosage, by a shift from one arsenical drug to another (such reactions are usually less intense after mapharsen) or in rare instances by a temporary interruption of arsenical in favor of heavy metal treatment Patients with early syphilis may properly be urged in view of the aim of radical cure " to discount a reaction which should if possible be eliminated in patients with late syphilis where "punishing" treatment is less desirable than prolonged well tolerated treatment

* Even sterile once-distilled water may contain dead bacteria, the proteins or toxins of which cause a slight reaction. Water should be freshly distilled and sterilized on the day of use

† Kolmer and Rule have recently shown that in experimental animals neoarsphenamine dissolved in a 5 per cent solution of sodium dehydrocholate is the same in toxicity and therapeutic efficiency as when dissolved in distilled water

The Angioneurotic Symptom-Complex

This term covers a variety of symptoms which may occur together with the nitritoid crisis or as isolated phenomena. The general similarity of the various symptoms to those occurring in angioneurotic edema is responsible for the name. The nitritoid crisis was aptly named by Millian because of the similarity of its symptoms with those caused by the inhalation of amyl nitrite.

The nitritoid crisis.—Actually during the injection of the drug, or within a few moments thereafter, the patient complains of feeling hot, of palpitation and of a sense of oppression in the chest. The first symptom is usually suffusion of the conjunctivae which should always be watched during the actual injection. If the injection is promptly interrupted at the first appearance of this symptom, the reaction will be mild. If however, the administration of the drug is continued, some or all of the following more alarming symptoms may appear cutaneous flushing, choking cough, vomiting (especially if treatment is given soon after a meal) severe cramp-like pain in the lower back (lumbar muscles?) and fall in blood pressure. More rarely the various angioneurotic phenomena of edema of the face lips, tongue and glottis, or a generalized urticarial eruption, occur Pain in the teeth and gums has been recorded either alone or as part of the nitritoid crisis. There may be syncope, with thready almost imperceptible pulse. In almost all instances the patient is frightened by a sense of impending collapse or death and indeed the condition may seem equally alarming to the physician Instances of death during the reaction have been reported, though we have never seen one. Even if untreated, the reaction usually passes off within 20–60 minutes, leaving the patient little the worse for his terrifying experience.

This type of reaction rarely follows the first injection of an arsenical If it occurs once it is likely to be troublesome with subsequent injections. It is especially common after arsphenamine and neoarsphenamine (frequency perhaps 0 1–0.5 per cent of all injections) much less frequent with silver arsphenamine and tryparsamide It does occur occasionally after bismarsen and sulpharsphenamine given intramuscularly Mapharsen is almost completely free from this reaction. Certain batches of arsphenamine or neoarsphenamine seem particularly prone to offend in this respect.

The cause of the angioneurotic reaction syndrome —In a most illuminating study Hirshfeld Hyman and Wanger have shown that the rapid intravenous injection of a large number of dissimilar substances (including arsphenamine) into animals is followed by an immediate train of symptoms. These include salivation vomiting, diarrhea, dyspnea, lessened coagulability of the blood, fall in blood pressure and even death. These reaction did not occur in animals in which the liver had previously been removed or excluded from the circulation. The authors suggest, therefore, that the primary disturbance is in the liver cells, that it is due to a physico-chemical cause, and that some potent and labile substance (histamine?) is liberated by or escapes destruction by the liver They term the reaction "speed shock. There is no doubt that the most frequent

cause of the nitritoid crisis after the arsphenamines is rapidity of injection in fact the reaction may be produced at will in almost any patient by rapid injection, or reduced in severity or even eliminated entirely in patients susceptible to it by very slow administration of these drugs

This is not the only cause however, since the reaction rarely occurs after tryparsamide or mapharsen, no matter what the speed of injection and in some patients susceptible to the arsphenamines, it does occur no matter how slowly the dose is given. That in part it is due to the drug is shown by the similarity of the symptoms (and in animals experimentally killed of the necropsy findings) to those produced by acid arsphenamine Oliver and Yamada have shown that the arsphenamines cause intravascular agglutination of red cells, and that *the symptoms and lesions of the acute* angioneurotic symptom complex are due to multiple minute emboli. As Schamberg and Wright put it, ' the cause is a physical one and is not dependent on the toxicity of the product(s) as determinable in test animals.

The prevention and treatment of the angioneurotic reaction complex—Adrenalin is the remedy par excellence for the nitritoid crisis and for the various angioneurotic phenomena associated with it. The rationale of its use is to combat the fall in blood pressure which accompanies the reaction. A small sterile syringe should always be available during treatment with any of the arsphenamines. *If this* reaction occurs 0 6 cc. (10 minims) of 1–1000 adrenalin solution given intramuscularly will usually afford prompt relief With the more serious reactions—the patient in syncopal shock, with very weak or absent pulse—*0.2–0.3* cc of 1–1000 adrenalin may be given *very slowly* by the intravenous route It is rarely necessary to repeat the adrenalin injection. The patient should be kept quietly at rest for an hour or so following even mild reactions with those more seriously ill, 24 hours of rest in bed is advisable

When the reaction has once occurred, its appearance must be watched for after all subsequent injections of the same product which originally caused it It may usually be prevented by one or more of several simple expedients

1 Give all subsequent injections of the arsphenamines very slowly through a fine gauge needle Be prepared to interrupt the injection at once on the appearance of conjunctival suffusion flushing choking etc.

2 If this fails to prevent the difficulty give 0 6 cc of 1–1000 adrenalin intramuscularly 5 minutes before the injection of arsphenamine (Caution —the use of adrenalin in patients with hypertension or cardiovascular syphilis may be dangerous) This preliminary injection of adrenalin usually prevents the reaction completely

3 If adrenalin is contra indicated if it fails to prevent the difficulty or if the patient finds the symptoms produced by adrenalin distressing the angioneurotic syndrome may usually be eliminated by a shift of drug from arsphenamine or neoarsphenamine to mapharsen or silver arsphenamine The reaction in question is much less common from these latter preparations than from other members of the arsphenamine series

After several injections have been given without reproducing the syndrome it may be possible to resume the use of the originally reactive

arsphenamine This is particularly true if an interval of several months has elapsed. If the attempt is made, however great care should be exercised to give the injection slowly

Stokes has suggested various other expedients for the prevention of this type of arsphenamine reaction He has utilized the principle of "anti anaphylaxis," i.e. the administration of one-tenth of the planned dose of arsphenamine and a delay of an hour before the remaining nine-tenths is given. He has also suggested the preliminary subcutaneous injection of 1-2 mgms. (1/60–1/30 grain) of atropin sulphate 20 minutes before treatment and more recently in reactive patients, the daily use during the period of arsphenamine treatment of 50 mgms. of ephedrin by mouth. We have tried all these expedients and agree with Stokes that in some instances they afford relief However in our hands the results obtainable from slow injection, adrenalin, a change in the arsphenamine product employed or all three, have proved so much simpler and so much more satisfactory that the more elaborate preventive procedures seem unnecessary

Shock like reactions (*Medical Shock'*) —Rarely one sees patients in whom the intravenous injection of an arsphenamine is followed either immediately or several hours later by a condition clinically similar to acute surgical shock. This is characterized by weakness, grayish cyanosis, cold clammy skin, nausea and vomiting, collapse and syncope the pulse is weak, rapid and thready, or even impalpable the blood pressure is lowered to alarming levels, or even as in three patients we have seen completely unobtainable (Weinberg) There is rapid dehydration diminished blood volume, increased hemoglobin and erythrocyte count in peripheral blood increasing blood nitrogen and sometimes anuria. Orr has termed this reaction "medical shock. It is not relieved by the use of adrenalin in contrast to the nitritoid crisis but in most instances symptoms may be promptly alleviated by the usual shock-combatting methods —complete rest, elevation of the foot of the bed warmth, and the slow intravenous administration of large quantities (2–3 liters) of sterile 10–15 per cent glucose solution or of normal saline solution and particularly by the administration of oxygen immediately the patient s condition becomes evident. This reaction has not been observed after mapharsen.

It is at least suggested by the experimental work of Hirano on the adrenal glands in animals poisoned with the arsphenamines and by the case reports of Rowntree and Hellfers detailing similar serious or fatal arsphenamine reactions in patients suffering from Addison s disease, that this reaction is due to acute adrenal injury

Arsphenamine Reactions Due to Myocardial Injury

When large doses of an arsphenamine are given to a patient with cardiovascular syphilis there may occur an immediate very severe and often fatal reaction This appears during the injection or within a very few minutes thereafter It is characterized by fainting, ashy gray-green pallor and profuse sweating the pulse becomes rapidly imperceptible the pa

TABLE 18A

TYPES AND ESSENTIAL CHARACTERISTICS OF POST ARSPHENAMINE DERMATOSES

Type of eruption	Special remarks	Evidences of visceral damage associated*	Expression of permanent sensitization	Further arsphenamine permissible
Urticarial	Part of angioneurotic reaction syndrome	0	0	Yes
Erythema of the Ninth Day (Erythematous, scarlatiniform)	Occurring early in treatment, sometimes after first or second dose. Accompanied by fever but no other constitutional symptoms. Infectious in origin?	Occasionally	0	Yes, try different product in minute dosage
Herpes simplex	Rare. Etiology unknown. Infection?	0	0	Yes
Herpes zoster	*Rare Etiology unknown.* Infection?	*0*	*0*	*Yes*
Macular (morbilliform)	Beware of more arsphenamine if these eruptions are associated with marked itching or if the lesions tend to be scaly	Unusual	± to ++++	Doubtful use great caution
Maculopapular (erythematosquamous)				
Papulovesicular	Different degrees of the same phenomenon Potentially serious	+ to ++++	++++	NO!
Vesicular				
Exfoliative				
Lichenoid	*Probably a variety of the above*	?	++++	*NO!*
"Fixed" exanthems	Not enough information available as to course under prolonged treatment	0	++++	Yes, probably
Purpura	Associated with blood dyscrasias	++++	Not known, but reactions prone to re-occur	NO!

* Especially renal damage blood dyscrasias, or hepatitis.

vented by adrenalin 0 6 cc intramuscularly) and can often be eliminated by a shift from one arsenical product to another (*e g. neoarsphenamine* to mapharsen or silver arsphenamine) Urticaria has no significance in further treatment Persistent use of arsenic does not result in more serious *dermatitides*

Herpes febrilis and herpes zoster are rare occurrences after all arsenical drugs, appearing a few hours or days after injection The mechanism of their causation is unknown. Certain individuals are unusually susceptible to herpetic lesions, which seem to occur with the slightest infection as for example an acute coryza. It is possible that their appearance after arsenical treatment may indicate the occurrence of fever due either to a break in the technique of administration (e g unsterile water) or the lighting up of a latent focus of bacterial or virus infection in the patient (Milian) At any rate the herpetiform lesions are not accompanied by other evidences of drug intoxication are not on a sensitization basis and do not necessarily recur after further treatment which need not be interrupted. Only symptomatic treatment is necessary

Reaction of the 5th–19th day (Erythema of the Ninth day—Milian) —In 1917 Milian described a reaction occurring approximately 9 days following the first dose of arsphenamine, and characterized by an erythematous skin eruption associated with malaise and a rise in temperature. He named this reaction *erythema of the 9th day* and thought it was due to a flare-up of a latent non-syphilitic infection (biotropism) Although extensively studied abroad, surprisingly little attention has been paid to this reaction in this country The best description of it is by Peters of the Johns Hopkins Clinic who has studied 54 patients, 67 per cent of whom were hospitalized and subjected to complete surveys. The following description is from this report. The reaction occurs from 5–19 days after the first injection (average 7.8 days) and may follow any of the trivalent arsenicals. It is characterized by a polymorphic erythematous, scarlatiniform or macular skin eruption accompanied by fever [temperature 38.3 – 40.5°C (101 –105°F)] sore throat, headache, malaise diarrhea stiffness of the neck and evidence of lymphoid hyperplasia. Its average duration is 6 days. It is twice as frequent in females as in males and occurs most frequently in patients with early syphilis (63 per cent of Peters' cases) In most cases, the fever subsides and the skin rash rapidly fades within a few days. Immediate complications which include nephritis, hepatitis hepatomegaly without jaundice occur in about a fourth of the patients and generally appear shortly after the onset of the skin eruption. If treatment with trivalent arsenicals is resumed within two weeks after the reaction appears, permanent intolerance develops in more than 77 per cent of patients If on the other hand, arsenical treatment is withheld until 4–8 weeks or more after the reaction subsides subsequent reactions which are for the most part mild occur in only 28 per cent of patients. Since this reaction has been noted in non-syphilitic individuals following treatment with the arsphenamines it is obviously not related to infection with *T pallidum*. Intercurrent infections are probably not a factor since they were not demonstrable in any of Peters carefully studied cases. In addition this reaction has been noted following drugs other than the arsphenamines, e.g. antipyrine sulfanilamide etc It must be considered, therefore as one of the systemic toxic reactions to the arsphenamines and one which may if not properly managed result in grave consequences so far as future antisyphilitic treatment is concerned Immediate treatment of

the reaction consists of rest in bed, forced fluids, intravenous glucose and discontinuance of arsenotherapy for at least one month after the skin eruption has subsided There is, however no contra-indication to the administration of heavy metals during or immediately after the reaction, an essential procedure when it occurs in a patient with early syphilis.

In some instances a generalized erythrodermia may be the forerunner of an exfoliative dermatitis in such patients intense itching and some scaling, especially in the flexor folds about the elbows and knees usually accompany the rash. Since it is often difficult to be certain of one's ground in this respect caution is the better part of valor Administration of the arsphenamines should be suspended until the rash has completely faded and resumed only with great caution (pp 106–107)

This or a nearly identical reaction is a common accompaniment of the massive arsenotherapy of early syphilis (cf Chapter XXXIII)

The major dermatitides (due to drug sensitization)* —Those rashes listed in Table 18A as macular morbilliform maculo-papular erythemato-squamous papulovesicular vesicular exfoliative and lichenoid are among the most serious disasters of arsenical therapy They have four usual features in common—generalized and often intolerable itching, *scaling of the skin associated constitutional symptoms and evidence of* visceral damage and the certainty of aggravation or recurrence after further arsenical treatment. The interval between treatment and the appearance of the rash is variable from a few hours to as long as 3 weeks The average is about 5 days. The eruption usually begins as a maculo-papular or vesicular dermatitis often limited at first to the extremities (especially the flexor folds) but rapidly spreading until the whole body (scalp face, trunk, extremities palms and soles) is involved. Underlying the individual papular or vesicular lesions may be a universal erythema with fine branny exfoliation. Intense edema of the face, and indeed of the entire skin (so that the thickness and appearance of the skin are comparable to the *tanned pigskin of a football) may occur In the milder cases, particularly* of the macular or maculo-papular type the process may stop with this and the eruption disappears in a few days. In the more severe and especially in the vesicular eruptions, marked scaling and exfoliation finally occur and the skin of the entire body is desquamated in large flakes. Often an entire palmar or plantar surface comes away intact The rash is accompanied by the most intense and distressing itching. Exfoliation is usually complete in 3–4 weeks, but sometimes takes much longer Occasionally a patient is seen in whom several distinct exacerbations occur the skin continuing to exfoliate periodically for several months

The mucosae as well as the skin may be involved in the exfoliative process *We have seen severe conjunctivitis* due to desquamation of the conjunctival epithelium temporary deafness from heaping up of exfoliated epithelial debris in the external auditory canal vaginitis diarrhea, with

* A rare manifestation of sensitization to arsphenamine is asthma (case reported by Klauder) We have never seen such an incident, but have seen asthma and urticaria occurring in a pharmacist from the inhalation of tryparsamide

large amounts of mucous, epithelial cells and, in more severe cases, blood in the stools edema and desquamation of the buccal surfaces and acute bronchitis

Associated evidences of generalized intoxication are present with varying degrees of frequency Fever malaise, and prostration are common. Renal damage, with albuminuria, cylindruria, more rarely hematuria and rapidly falling kidney function occurs in some patients. Jaundice (arsenical hepatitis?) and polyneuritis are relatively infrequent complications. Injury to the bone marrow, sometimes to the extent of associated purpura or agranulocytic angina, often occurs, manifested even in the absence of suggested symptoms by leucopenia, a decrease in neutrophilic granulocytes eosinophilia and an increase in monocytes. This is probably responsible for the greatly increased susceptibility of patients with this form of arsphenamine dermatitis to infection (especially skin infections—boils, carbuncles, etc.—and bronchopneumonia, from bacterial invasion of the denuded bronchial mucosa) and for their intolerance to interference with foci of infection already present. Attempts at removal of infected tonsils of abscessed teeth, etc. during the course of an arsphenamine dermatitis, may as Stokes and Cathcart have pointed out, lead not only to an exacerbation of the dermatitis but even to death from generalized bacterial infection. These phenomena are surely due to the interference with the body's ability to resist bacterial infection as a result of bone marrow damage.

The prodromal symptoms of the major post arsenical dermatitides —Owing to the incapacity produced by and the risk of life from the major post-arsenical dermatitides, it is of paramount importance to consider the possible significance of prodromal symptoms. These are often lacking the appearance of an exfoliative dermatitis comes with unexpected and explosive force. In some patients however reactions may occur after each of several doses before the final disaster Generalized itching without any obvious skin rash unexplained fever for 24–48 hours or longer after each injection malaise lasting for several days and out of all proportion to the size of the dose administered and mild and apparently insignificant eruptions —all these may precede the major dermatitis by several weeks. It should be unvarying *routine to inquire for reactions before the administration of each dose, and to ask the specific question, "Did the last dose cause any itching or breaking out?"* The occurrence of any of these phenomena calls for immediate suspension of treatment and a general survey of the patient.

Factors contributory to the major dermatitides The incidence of the major post-arsenical dermatitides has been recently determined by the C C G and is presented in Table 19 As shown in this table these reactions occur with varying frequency after different arsenical preparations. Sulpharsphenamine is the worst offender Arsphenamine neoarsphenamine, silver arsphenamine and mapharsen are responsible in lessening order of frequency Indeed, the incidence of post-arsenical dermatitis originating from mapharsen is negligible though patients sensitized by

TABLE 19
INCIDENCE OF THE MAJOR POST ARSPHENAMINE DERMATITIDES
(From C C G)

Drug	Number of injections	Incidence of dermatitis per 1000 injections
Arsphenamine	105 942	90
Neoarsphenamine	30 779	81
Tryparsamide	19 964	15
Bismarsen	8 552	23
Sulpharsphenamine	7 912	1 39
Silverarsphenamine	3 848	52
Mapharsen	56 290	053

Data of U.S. Navy 1935 to 1938 inclusive.

other trivalent arsenicals may also develop dermatitis after mapharsen Our experience differs from the above insofar as we have found neoarsphenamine to be more frequently at fault than arsphenamine

Whether the arsenicals are used alone or in combination with a heavy metal makes no difference in the incidence of these reactions. Nor are they especially prone to occur in patients with pre-existing renal damage and hence by implication with impaired ability to excrete the drug.

Dosage technique of administration impurities in the drug and manufacturers lot of drug employed play no basic part in the development of the reaction Dermatitis is as likely to occur after small as after large doses. Klauder and others have suggested that infiltration of the tissues with the drug as a result of faulty intravenous technique may sensitize the patient and predispose to a subsequent attack of dermatitis In spite of the support accorded this hypothesis in recent experimental work presently to be discussed it is not entirely in accord with our own experience and that of Schoch, in which dermatitis has more often appeared in patients who had not suffered such an accident

Dermatitis tends to appear early in treatment the majority of all cases occurring within the first dozen or so injections Both Stokes and ourselves have seen examples of exfoliative dermatitis after the first dose and this seems to impair the validity of the conclusion that the reaction is due to drug sensitization. Further study is necessary as to this point

The race sex or age of the patient (except that infants and young children seem relatively immune) play no part in the etiology of post-arsenical dermatiti nor does the type or duration of syphilitic infection. Pre-existing focal infection has little or nothing to do with the development of the major dermatitides though as we have indicated interference with such foci during the course of the reaction may be provocative of disastrous results

Sensitization as a cause of the major dermatitides —The earliest clinical observations on the severe post-arsenical dermatitides, especially exfoliative dermatitis, showed clearly that subsequent attempts to give an arsphenamine product, no matter how long the interval or (*within limits*) *how small the dose* were productive of a second attack. Thus in attempting skin sensitization tests on patients who had suffered from this type of reaction Robinson and Moore have produced a second attack of generalized dermatitis with a dose of approximately .005 mgm. of arsphenamine (0.1 cc of a 1–2000 solution injected intradermally) as long as 6 years after the original dermatitis. This phenomenon, certainly not due to the toxicity of the infinitesimal quantity of arsphenamine administered, can hardly be interpreted otherwise than as evidence of allergic sensitization to the drug or to some compound formed or elaborated by it within the body

This sensitization is usually group specific (Moore and Keidel, Frei and Mayer) i.e. it extends to all members of the trivalent arsenical group but not to inorganic or pentavalent organic arsenical drugs Clinical experience indicates, however that in rare instances it may be drug rather than group specific, i.e., a rash caused by arsphenamine may not be reproduced after neo- or silver arsphenamine or mapharsen.

Ingenious experiments by Frei and by Nathan and Munk in human beings, by Frei and Sulzberger and particularly by Landsteiner and Jacobs in guinea pigs demonstrated the sensitization of the skin of both man and animals against the arsphenamines by means of intradermal injections of minute quantities of the drugs. The type of sensitization differs from that caused by protein substances in that its demonstration by the passive transfer method fails and that a generalized anaphylactic state is not induced. Furthermore, while sensitization may be prevented by appropriate methods, there is no clear evidence that desensitization can be accomplished once the sensitized state has developed

The practical value of skin tests as a means of demonstrating arsphenamine sensitization —Numerous attempts have been made to demonstrate the hypersensitive state to arsphenamine by means of skin tests (scratch intradermal and patch) None is of much practical value By the intradermal method normal non-syphilitic individuals may develop a delayed inflammatory reaction at the site of injection this is also observed in non-reactive syphilitic patients under treatment. Violent early reactions develop in most patients known to be sensitive to arsphenamine *but not in all* and such reactions also occur in a high proportion of allergically unstable (hayfever) non-syphilitic patients never treated with arsphenamine. Finally this method of testing is dangerous in that it may sensitize a patient who subsequently must receive therapeutic injections of arsphenamine

More recently Schoch has claimed specificity for patch testing, on the basis of experience with 8 cases of post-arsphenamine dermatitis. Robinson and Moore have repeated his experiments on some 60 patients with previous dermatitis and about 100 normal controls In their hands the results are the same as with intradermal testing, i.e. an occasional positive

reaction in a normal control and numerous negative results in patients known to be sensitive. However in a more recent study of patch testing, Robinson has shown that while the arsphenamines are contra-indicated in every sensitized person in whom such tests are positive approximately *one-third of those in whom they are negative can under proper precautions* receive further treatment with arsenicals. At present, therefore hyper sensitivity to the arsphenamines cannot be definitely shown through intradermal skin testing and can only be approximated by patch testing

The demonstration of arsenical hypersensitivity by intravenous testing.—Not infrequently the situation arises that the practitioner or indeed the expert, is in doubt as to whether a given instance of post arsenical dermatitis is due to sensitization or to some other cause. *If the former the therapeutic use of these drugs is forever banned If the* latter more arsenic may be given In order to determine this, advantage may be taken of the fact that the intensity of the dermatitides due to sensitization is roughly proportionate to the dose of drug injected.

After the reaction has completely subsided and an additional interval of 2–3 months has been allowed to elapse, the patient s hypersensitivity may be cautiously tested out with minute doses of an arsenical drug given intravenously A different product than that which caused the original reaction should be chosen to allow for the possibility that the first accident may have been drug rather than group specific. Before it is given, the patient should be patch tested with it. If the patch tests are positive, intravenous testing is contra-indicated. If they are negative a very small initial dose, e.g 0 025 gm of the test arsphenamine (or 0 002–0 005 gm of mapharsen) is given. This is increased by equally small increments until the patient s tolerance or lack of it, is established If the first attack was due to sensitization, the first or early injections of the trial series will be followed by (a) generalized itching without a visible rash, (b) a mild dermatitis generally reproducing though with less intensity the characteristics of the first attack (c) malaise—a "knocked-out feeling—out of all proportion to the size of the dose injected, and persisting for several days or (d) fever following each injection and lasting 24–48 hours or longer If either of the latter two circumstances occurs, a white and differ ential blood count should be done Leucopenia, a decrease in neutrophilic granulocytes, eosinophilia, or an increase in monocytes indicate definite trouble

If any of these phenomena occur the idea of further trivalent arsenical therapy at any time in the future must be permanently abandoned. The patient should be told of the situation so that if he subsequently falls into the hands of another physician he will be able to prevent the admin istration of further arsphenamine given in *ignorance of his earlier reaction Failure to observe these precautions may cause the patient s death.*

Should none of these symptoms appear the dosage may be cautiously increased until an average therapeutic level is reached somewhat in ac cord *with the suggestions of Table 20 This method of testing sensitivity* should be applied only when one is in doubt as to the original rash. Hyper sensitivity may be definitely assumed to be present if the original eruption

TABLE 20

SUGGESTED OUTLINE FOR TESTING FOR ARSENICAL HYPERSENSITIVITY

1. Wait for all signs of original dermatitis to subside.
2. Wait 2–3 more months.
3. If original reaction was due to arsphenamine, try neo- or silver arsphenamine or mapharsen. If due to neoarsphenamine, try arsphenamine, silver arsphenamine, or mapharsen.
4. Do patch tests with the drug to be tested. If positive, intravenous testing contra-indicated.
5. If patch testing is negative, conduct experimental treatment as follows

Week	Dosage of arsphenamine or silver arsphenamine	Neoarsphenamine	Mapharsen
1	0.025 gm.	0.025 gm.	0.005 gm.
2	0.05 gm.	0.05 gm.	0.010 gm.
3	0.075 gm.	0.1 gm.	0.015 gm.
4	0.1 gm.	0.15 gm.	0.020 gm.
5	0.125 gm.	0.2 gm.	0.030 gm.
6	0.15 gm.	0.3 gm.	0.040 gm.
7	0.2 gm.	0.45 gm.	0.050 gm.
8, etc.	0.3 gm.	0.6 gm.	0.060 gm.

6. Stop permanently if itching, dermatitis, undue malaise, fever or alterations in leucocytic blood picture occur.

itches intensely, if it contains vesicles, or if it scales or exfoliates. To such patients further arsphenamine is permanently forbidden; tolerance testing is dangerous and should be omitted.

The prognosis of the major post arsenical dermatitides.—While the severe post-arsenical dermatitides are extremely serious treatment complications, their prognosis is not as grave as was formerly believed. Among 189 cases observed by the C.C.G. there were only 4 fatalities, a mortality of 2.0 per cent. One of the four patients had accompanying toxic hepatitis and two others hemorrhagic encephalitis. In the cases of dermatitis unaccompanied by other damage as a result of arsenic, death is generally due to the unusual susceptibility to infection (septicemia, broncho-pneumonia), to uremia, or to the complications of hepatic or bone marrow damage.

The treatment of the major dermatitides.—The patient should be hospitalized promptly, if possible, and placed at complete rest in bed. Itching may be controlled in part by sterile olive oil rubs or by the colloid bath.* If these measures fail, the application of x-ray to the most bother

* Colloid baths may be purchased ready for immediate use or can be prepared according to the following technique of Stokes:

"Boil 3 cups of oatmeal in 2 quarts of water until a porridge is formed. Do not burn. Set aside to cool. Fill the ordinary bath-tub half-full of water (temperature 100°F.) and dissolve in it 1 teacupful of baking soda. Pour the porridge into a cheesecloth bag, tie the mouth securely, and by washing it about in the water dissolve out the mucilaginous material, leaving the residue in the bag. The water should become whitish and opalescent. Raise the water temperature to 98°F., by bath thermometer (not by the hand or elbow feel). Then, and only then, may the patient enter the bath! In the ordinary bath-tub it is impossible for the patient to lie completely ex

reaction in a normal control and numerous negative results in patients known to be sensitive. However in a more recent study of patch testing, Robinson has shown that while the arsphenamines are contra-indicated in every sensitized person in whom such tests are positive approximately one-third of those in whom they are negative can under proper precautions receive further treatment with arsenicals. At present therefore hyper sensitivity to the arsphenamines cannot be definitely shown through intradermal skin testing and can only be approximated by patch testing.

The demonstration of arsenical hypersensitivity by intravenous testing.—Not infrequently the situation arises that the practitioner or indeed the expert, is in doubt as to whether a given instance of post-arsenical dermatitis is due to sensitization or to some other cause. If the former the therapeutic use of these drugs is forever banned if the latter more arsenic may be given. In order to determine this advantage may be taken of the fact that the intensity of the dermatitides due to sensitization is roughly proportionate to the dose of drug injected.

After the reaction has completely subsided, and an additional interval of 2–3 months has been allowed to elapse, the patient's hypersensitivity *may be cautiously tested out with minute doses of an arsenical drug given* intravenously A different product than that which caused the original reaction should be chosen, to allow for the possibility that the first accident may have been drug, rather than group specific *Before it is given, the patient should be patch tested with it. If the patch tests are positive* intravenous testing is contra-indicated. If they are negative a very small initial dose e.g., 0 025 gm. of the test arsphenamine (or 0.002–0.005 gm. of mapharsen) is given. This is increased by equally small increments *until the patient's tolerance or lack of it, is established. If the first attack* was due to sensitization, the first or early injections of the trial series will be followed by (a) generalized itching without a visible rash (b) a mild dermatitis generally reproducing, though with less intensity the characteristics of the first attack (c) malaise—a "knocked-out" feeling—out of all proportion to the size of the dose injected, and persisting for several days or (d) fever following each injection and lasting 24–48 hours or longer If either of the latter two circumstances occurs, a white and differential blood count should be done Leucopenia, a decrease in neutrophilic granulocytes eosinophilia, or an increase in monocytes indicate definite trouble

If any of these phenomena occur the idea of further trivalent arsenical therapy at any time in the future must be permanently abandoned. The patient should be told of the situation, so that if he subsequently falls into the hands of another physician he will be able to prevent the administration of further arsphenamine given in ignorance of his earlier reaction. *Failure to observe these precautions may cause the patient's death.*

Should none of these symptoms appear the dosage may be cautiously increased until an average therapeutic level is reached, somewhat in accord with the suggestions of Table 20 This method of testing sensitivity should be applied only when one is in doubt as to the original rash. Hyper sensitivity may be definitely assumed to be present if the original eruption

mental work is necessary before this is proved and at present the use of glucose in this situation is entirely empirical.

Calcium salts have also been proposed for the treatment of post-arsphenamine dermatitis, presumably because of their probable value in patients with hepatic damage because of the fairly frequent association of these two evidences of arsphenamine toxicity, and because of their supposed effect in decreasing capillary permeability and lessening exudation in other allergic diseases. So far as we are aware, there is no definite experimental evidence of the favorable action, if any, of calcium indeed Mu has shown that it has no effect in preventing the development of arsphenamine sensitization in guinea pigs. We have employed calcium gluconate 1.0 gm (10 cc. of a 10 per cent solution) in daily intravenous injections in patients with dermatitis. It is difficult to be sure that improvement is due to this form of treatment, but we have the impression that it is of some value certainly more than sodium thiosulphate. Schamberg and his associates have suggested that the virtues of calcium and thiosulphate therapy might be combined by the use of a new preparation calcium thiosulphate. Reports as to its efficacy are not yet available.

Sodium thiosulphate was first suggested for the treatment of arsenical dermatitis by Ravaut and has been popularized in this country by McBride and Dennie. It has been recommended for all types of arsenical intoxication, for other types of heavy metal poisoning and even for the treatment of seroresistant syphilis. There has been very little experimental evidence either to support or to deny the claims made for the drug and such evidence as has been presented is confusing and contradictory. In a recent careful experimental study including a complete review of the literature Muir and her associates found that sodium thiosulphate was of no value in arsenical poisoning in rabbits and if it had any value in arsenical intoxication in humans it was not because it combined as such with the arsenicals but because it was transformed into intravital sulphur. They point out that neither sodium thiosulphate nor any similar sulphur compound can act chemically on an arsenical compound with the structure of the arsphenamines, that is, with a double bond between the arsenic. Theoretically such action could occur after the arsphenamines had been reduced to arsenoxide. However even after this reduction has occurred the pH of the tissues is too alkaline to permit a combination of the two compounds to occur. These experimental findings offer an explanation for our clinical experience that sodium thiosulphate is of no value in the treatment of arsenical dermatitis.

Vitamin C deficiency as a cause of and therefore its administration in the treatment of arsenical dermatitides has received an increasing amount of attention during the past few years. Unfortunately most of the literature deals with clinical impressions and so far the experimental work has been confusing. In the most convincing study to appear so far Cohen could find no relationship between the vitamin C content of the diet and the development of cutaneous reactions to neoarsphenamine. Cormia feels however that vitamin C is distinctly beneficial in treatment and even that some sensitive patients may be apparently desensitized by the

repeated intravenous injection of massive doses (500 mgms daily) of the vitamin.

Fixed" arsphenamine exanthems —These lesions first described by Fuchs are an expression of local rather than of general sensitization of the skin. The usual description is of a sharply localized erythematous plaque itching intensely appearing in the identical location a few hours after each injection of an arsenical. Rarely the exanthem may consist of reddening and itching of one conjunctiva after each dose. The plaque may disappear between injections, leaving a pigmented spot or it may be present continuously becoming eczematous in character but more acutely inflamed after each dose. Reactions of this type are rare we have seen only a few "Fixed eruptions have also been observed following tryparsamide. They are uncommon only a few cases having been reported

Further arsenical treatment in such patients should proceed with caution The local reaction may be the precursor as in a fatal case reported by Stokes and Cathcart, of a general sensitization of the skin and an explosive outbreak of generalized dermatitis.

Purpuric eruptions —Whether as isolated phenomena or as part of a dermatitis of other types, purpuric lesions following an arsphenamine are an expression of toxic injury to hematopoiesis For their significance and management, the section of this chapter on blood dyscrasias should be consulted

Post arsphenamine pigmentation —Diffuse pigmentation of the skin with or without palmar and plantar hyperkeratosis, has been described after arsphenamine as well as after the prolonged use of inorganic arsenical drugs It is sufficiently rare that no case has been seen in our clinic. In some instances, however we have seen persistent pigmentation (or in some instances depigmentation vitiligo) after the healing of a post arsphenamine exfoliative dermatitis. Nothing can be done about it.

Argyria from Silver Arsphenamine

We have seen six or seven patients all of whom had been under prolonged treatment with silver arsphenamine and bismuth who slowly developed a dirty grayish blue discoloration of the skin especially of the face and neck *associated with an intense pigmentation of the gum margins* and the buccal mucosa. The latter is indistinguishable from that produced by bismuth alone the discoloration of the skin resembles that of mild examples of argyria. Spiegel has seen similar patients and has demonstrated by spectroscopic examination of the skin that the pigment is silver

The argyria is always mild and does not appear at all until a considerable quantity of both drugs has been given *Apparently a minimum of* 20–25 injections (to a total of 6 0–8 0 gms) of silver arsphenamine must precede the appearance of the pigment deposit and further argyria apparently does not occur unless silver arsphenamine and bismuth are given simultaneously Some interaction between the two drugs is neces-

sary Many patients never develop argyria even when given many more than 25 injections of silver arsphenamine.

In our experience the development of argyria has not been a serious drawback to the use of silver arsphenamine. The pigmentation is always mild conveying only the impression that the face is slightly dirty and it never reaches the intense blueness seen after silver nitrate. The possibility of its development must be kept in mind if the prolonged administration of silver arsphenamine and bismuth is contemplated

Having once occurred the pigmentation is permanent. Sodium thiosulphate is of no value in this condition.

Reactions from the Arsphenamines in the Nervous System

Neurorecurrence —This phenomenon once thought to be due to the arsphenamines, is now known to be due instead to syphilis It is discussed in Chapter XXII.

Polyneuritis —Peripheral neuritis, reviewed in an article by Beeson, is a rare complication of treatment with the arsphenamines.* Its production by various metals, especially lead and arsenic, has been known for many years. Its infrequency after the arsphenamines is shown by the fact that in the administration of more than 900 000 injections of these drugs to some 45 000 patients, we have seen only a dozen or so examples all of which followed sulpharsphenamine or neoarsphenamine predominantly the former The symptoms usually arise only after a good deal of treatment—20 or more injections—has been given, and consist at first of numbness burning, and tingling of the feet and hands. In the early stages there may be no demonstrable objective changes or only tenderness on palpation of the calf muscles may be found The minor symptoms may clear promptly when the drug is withdrawn. In rare instances, the lesion progresses to the point of grave muscular weakness wrist and foot drop loss of deep reflexes atrophy, and stocking and glove anesthesia. Recovery is very slow and often incomplete. In our experience the reaction usually occurs alone more rarely it is associated with dermatitis. The mechanism by which the peripheral nerve involvement is produced is quite unknown.

Treatment of arsenical polyneuritis includes the permanent abandonment of the drug In addition the daily parenteral administration of large doses (50–100 mgms) of thiamin chloride (vitamin B_1) for at least 10 to 14 days may prove beneficial. Orthopedic treatment may be necessary to prevent permanent deformity

Confusion in diagnosis may arise from the fact that in exceptionally rare instances, peripheral neuritis may be due to syphilis (symptoms usually in association with florid secondary syphilis and almost always present before treatment) or to bismuth. We have recently seen two patients with polyneuritis in which all possible causes except bismuth could apparently be eliminated.

Hemorrhagic encephalitis —This is a very grave and fortunately uncommon complication of arsphenamine therapy Curiously enough, and

* When used by standard, not massive, methods (cf Chapter XXXIII)

repeated intravenous injection of massive doses (500 mgms. daily) of the vitamin

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there may be a few convulsions which cease and the patient recovers In some cases ending in recovery, loss of memory has occurred which has continued as long as a fortnight.

The characteristic pathologic feature of this reaction consists in edema of the brain with multiple punctate or small ring-formed hemorrhages. There is no tendency to hemorrhage elsewhere in the body and such pathologic alterations as may exist in the viscera are apparently unimportant. The mechanism of production of this type of reaction is as yet unknown but is probably related to the size of the dose injected in view of its frequency after massive doses in the 'five-day' treatment.

Schamberg and Wright advise the following treatment for encephalitis hemorrhagica. We cannot testify to its efficacy in view of our lack of personal experience.

Any patient who develops (severe) headache should be immediately confined to bed. Spinal puncture should be performed with withdrawal of at least 50 cc. of fluid Venesection withdrawal of 60–100 cc of blood should be performed. The bowels should be thoroughly purged and large doses of bicarbonate of soda should be given. Subcutaneous injections of adrenalin solution (1–1000) should be given in 5 minim doses every 4 hours during the day It is well to employ inhalations of oxygen inasmuch as there is some reason to believe that an anoxemia of the brain is associated with this complication.

Transverse myelitis —A number of cases have been reported (as, for example, by Scott and Reinhart) in which the intravenous injection of an arsphenamine has been followed within a few hours or days by a complete, flaccid paraplegia, which later becomes spastic. We have seen several similar instances. In our experience this accident is usually due to therapeutic shock involving a previously latent syphilitic endarteritis of the vessels of the cord, although in certain instances proof of this is lacking. The prognosis for recovery of function is poor

Ocular damage —For the first few years following their introduction there was considerable controversy concerning the toxicity of the arsphenamines for the optic nerve. During the past twenty five years it has become universally accepted in this country that ocular damage is caused only by the pentavalent arsenicals (tryparsamide) and never by the trivalent arsenicals unless they are injudiciously used in patients with pre-existing syphilitic optic neuritis. Recently Skirball and Thurmon have reported optic neuritis occurring in 2.7 per cent of all patients with early syphilis following the administration of arsphenamine. Their observations are as yet unconfirmed It seems incredible, if ocular damage following arsphenamine therapy occurs as frequently as they claim that it has not been detected by numerous other clinicians. It has never been observed among the thousands of patients in our clinics.

Blood Dyscrasias

The relative rarity of the blood dyscrasias due to the arsenical drugs is fortunate, since they are among the gravest of treatment complications. They are not however so uncommon as published reports indicate. We

classify all such patients, by means of repeated blood studies as promptly as possible

The mechanism of production of the blood dyscrasias.—The benzene radical of the arsphenamine molecule has been thought to act directly on the bone marrow, if this is true the mechanism of granulocytopenia and of aplastic anemia seems clear The type of reaction is dependent on the degree of damage the leucopoietic elements being injured first, the erythropoietic elements only by more intense insult The symptoms in those cases of pure thrombocytopenia are however too acute in onset to be due to bone marrow damage and it is probable that the arsphenamines exercise some deleterious effect on the platelets in the peripheral circulation This appears to be a regular phenomenon (Mu) though not to the critical level of permitting hemorrhage

In 2 of 6 cases of granulocytopenic purpura, one following neoarsphenamine and the other bismarsen, Falconer and Epstein were able to precipitate a second attack by the administration of small amounts of neoarsphenamine, 0 075 and 0 015 gm respectively This suggests that in some persons this reaction may be a sensitization phenomenon.

All the blood dyscrasias tend to appear late in the course of treatment, after many injections have been given Excessive dosage of drug plays no apparent rôle.

Treatment of the blood dyscrasias.—In the thrombocytopenic group no special treatment is indicated Transfusions, sodium thiosulphate calcium etc. have all been employed but untreated patients have recovered as rapidly and completely The risk to life appears to be small.

When agranulocytosis is present, whether as an isolated phenomenon *or as a part of an aplastic anemia no treatment measures appear to have* been effectual until the introduction of nucleotide therapy by Doan and his co-workers and by Jackson and his associates Prior to this, most of the cases were either rapidly fatal or sufficiently mild to warrant merely symptomatic treatment. With pentose-nucleotide strikingly favorable results have been obtained in the agranulocytic anginas produced by the arsphenamines as well as in those due to other causes the mortality rate having fallen from 90 to 25 per cent. This substance apparently acts as a direct stimulant of leucopoiesis It is administered in solution either intravenously or intramuscularly as the gravity of the situation seems to demand The dosage is 10–20 cc. daily A response visible in the blood picture usually occurs by the fifth day of treatment. Clinical improvement with temperature falling to normal and rapid healing of the necrotic angina, parallels the improvement in the blood picture

When aplastic anemia is present, repeated transfusion may be a life *saving measure by tiding the patient over* until spontaneous recuperation of bone marrow function has occurred, or until it can be stimulated with pentose-nucleotide

Subsequent antisyphilitic treatment in patients with blood dyscrasias.—When once a reaction of this sort has occurred all the arsphenamines are permanently barred. Attempts have been made to renew treatment but only in one instance (Bock) has this been successful.

The second attack may be fatal. Recently Falconer and Epstein have reported the successful administration of mapharsen following 5 cases of purpura hemorrhagica, 2 caused by neoarsphenamine, 3 by bismarsen. Goldberg has also used mapharsen successfully in 1 case of agranulocytosis following neoarsphenamine. In our clinic C F Mohr has successfully given mapharsen to 4 of 5 patients with previous thrombocytopenic purpura following an arsphenamine. There is no information available as to the ability of patients with blood dyscrasias to take tryparsamide, and, until there is further evidence that mapharsen is uniformly well tolerated in such patients, it is best because of the extreme gravity of the situation to leave clinical experimentation with further arsenotherapy in the hands of the expert rather than the practitioner The use of the heavy metals is not contra-indicated.

Post Arsphenamine Jaundice

Jaundice is a fairly frequent complication of arsphenamine therapy Estimates of its incidence vary Among the patients of the C.C G it occurred 178 times following approximately 175 000 injections, a rate of 1 to 1000 (Table 22) In contrast, Cook and Wingo of the U S. Navy found that it occurred only 25 times following over 1 000 000 injections, an approximate incidence of 0.25 per 1000 Since both groups of patients were treated during the same years and since males are more prone to develop jaundice than females, the reason for this discrepancy is not evident. Their large number of carefully followed cases makes the figures of Cook and Wingo the more authoritative.

The rôle of the various arsenicals in causing jaundice is shown in Table 22. As shown in this table, neoarsphenamine is the worst offender followed by arsphenamine, sulpharsphenamine and silver arsphenamine in the order named. This is in agreement with our experience except that

TABLE 22

INCIDENCE OF POST-ARSPHENAMINE JAUNDICE (From C.C.G)

Drug	Number of injections	Rate per 1000 injections
Arsphenamine	104 942	1 16
Neoarsphenamine	30 779	1 20
Tryparsamide	19 964	25
Bismarsen	8 552	12
Sulpharsphenamine	7 912	88
Silverarsphenamine	3 848	78
Mapharsen	56 290	—

Data of U.S. Navy 1935 to 1938 inclusive.

occurs in syphilitic patients under treatment more frequently than in non-syphilitics (in the Johns Hopkins Hospital eight times as frequently) though certain German evidence to be discussed presently disagrees with this statement (2) that it is more frequent following certain arsenicals than others e.g. with neoarsphenamine twice as frequent as with arsphenamine, (3) that in experimental animals, large doses of the arsphenamines (greatly exceeding those used in clinical practice) may cause central necrosis of the liver lobules, though never to the extent of producing acute yellow atrophy (4) that arsphenamine is known to be stored in the liver (5) that jaundice is apparently more frequent in patients in whom, for unknown reasons, the rapidity of excretion of the arsphenamines is impaired. It has been suggested by one group of observers (Bailey and MacKay) that the toxic effect of arsphenamine for the liver is increased by low carbohydrate and high fat diets. Craven contradicts these conclusions and shows by experiment that high fat and protein diets, particularly the former, protect against hepatic damage and that high carbohydrate diets are contributory Messinger and Hawkins have found, also by experimentation that protein is most effective in preventing liver damage from arsphenamine that carbohydrates rank next in this regard, and that a high fat diet is decidedly deleterious. Miller Ross, and Whipple, working with chloroform poisoning in dogs, confirm the protective action of protein in preventing liver damage and offer evidence to show that methionine and cystine are the specific protein protecting factors.

Approaching the problem from a different angle Soffer found, among other changes, marked hypoglycemia in 3 of 11 dogs acutely poisoned by arsphenamine. This he thought was due to the inability of the injured liver to convert lactic acid into glycogen and thereby make it available as a source of blood sugar

It is generally agreed—and in this much of the supposed protective effect of one or another type of diet we concur—that jaundice is more frequent in the clinic than in private practice, presumably because patients of the latter group are better fed.

Against the theory that the arsenical drug plays the major part in the complications are four inescapable facts (1) that jaundice is only rarely associated with such definite forms of arsphenamine toxicity as the immediate angioneurotic complications or the delayed dermatitides (2) that jaundice appears, as shown in Fig 10 at such variable intervals after treatment, whereas the excretion of arsphenamine is known to be nearly complete in the average patient within a week or two after treatment, and in jaundiced patients there is no satisfactory evidence of arsenic retention in the liver or elsewhere (3) that many patients have continued to receive arsphenamine throughout the whole course of the icterus without obvious ill effect and (4) that in practically all instances the patient is able after recovery from jaundice to take more arsphenamine without any evidence of recurrent hepatic damage. Of the 81 patients in Soffer s study who were subsequently treated only 2 developed a second attack of jaundice

Some support especially from Milian, has been available for the viewpoint that post-arsphenamine jaundice is usually due to syphilis, rather

than to arsphenamine and that it represents, in effect, a hepatorecidive analogous to the similar process in the nervous system. This conclusion is based on two facts —that most of the patients have syphilis and that in the hands of one observer who has had the temerity to continue arsphenamine throughout the course of the complication the jaundice is reported to improve more rapidly than in patients not so treated and that in any case, more arsphenamine does no harm. Against this view may be opposed the following facts —that jaundice has been observed in non-syphilitic persons treated with the arsphenamines for other causes that it usually occurs relatively late in treatment after the patient has had a number of injections of the drug, often in combination with a heavy metal that since arsphenamine is actually stored in the liver it is difficult to see how treponemes could persist alive in this tissue during prolonged treatment, to erupt into activity actually during treatment, when similar behavior on the part of the virus is not observed elsewhere in the body that jaundice occurs with equal frequency in patients with early and late syphilis that in patients dying of acute yellow atrophy the pathologic lesion is extreme central necrosis of the liver lobules, a lesion rarely produced by syphilis and that the subsequent course of patients with post-arsphenamine jaundice is quite different from that of patients with definite hepatic syphilis. To our minds it is possible that a very few instances of post arsphenamine jaundice may be due to syphilis. These are the cases in which jaundice appears promptly after the first few injections of arsphenamine i.e. so-called early jaundice in contrast to the late variety occurring late in treatment and weeks after the last dose. If this is the case the jaundice is probably a Herxheimer effect, due to an already existing hepatic syphilis, rather than to a hepato-recurrence. We should not know how to identify the latter and we could not even be certain of the former unless the diagnosis of hepatic syphilis was obvious before treatment.

The evidence that post-arsphenamine jaundice is due neither to syphilis nor to arsphenamine is based largely on epidemiologic studies, which are, however most convincing. It is generally agreed that since World War I there has been a considerable increase in the incidence of so-called acute catarrhal jaundice and of acute yellow atrophy in non-syphilitic patients. Numerous observers have pointed out the tendency of the former of these to occur in waves and the same phenomenon has been repeatedly noted with post-arsphenamine jaundice. The most striking epidemiologic data are those presented by Ruge from the German Navy He shows (Fig. 11) that since the War the increase in the incidence of post-arsphenamine jaundice almost exactly parallels the increased incidence of so-called catarrhal jaundice in non-syphilitic individuals who were not, of course, receiving arsphenamine. He points out further that the two diseases are clinically identical. He believes that they are due to the same etiological infectious agent, which is not as yet definitely known, but which he suggests may belong to the paratyphoid group of organisms. The spirochete of Weil s disease has not been found in spite of repeated search by Ruge and others.

The evidence available inclines us to feel that in most instances post arsphenamine jaundice may be due to one or a combination of all these factors, and that it probably represents an acute infectious disease in a patient whose liver function is subject to the added strains of syphilis and of metabolizing arsphenamine. In a few patients especially those with livers seriously damaged from some other cause, such as pregnancy, the direct toxic effect of arsphenamine may result in acute yellow atrophy

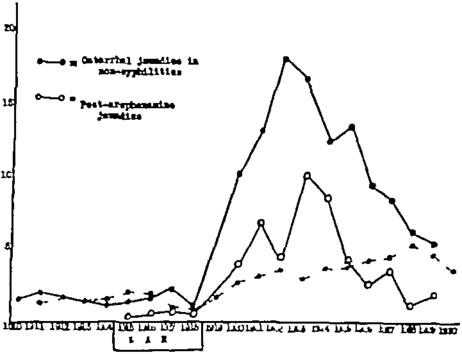


FIG 11 —The Parallelism between the Incidence of So-called Catarrhal Jaundice in Non-syphilitic Patients and of Post Arsphenamine Jaundice (Admissions per 1000 Strength) in the German Navy 1910–1929 (After Ruge.)

(*The lowermost line of dashes between open circles represents the incidence per 1000 strength of acute catarrhal jaundice—acute cholangitis—in the United States Navy from 1911–30. These data were obtained from the Annual Reports of the Surgeon General of the Navy The curve shows the same rising tendency, though not to the same extent, as in the German Navy Evidently the disease causing the clinical picture of acute catarrhal jaundice has shown a world wide increase since 1918.*)

The treatment of post arsphenamine jaundice —It is wisest to place patients with post-arsphenamine jaundice at rest in bed, especially until one can be certain of the extent of the hepatic damage Treatment is symptomatic only Sodium thiosulphate is, so far as we can see of no value at all Ellsworth working in the Johns Hopkins Hospital has shown that in post-arsphenamine jaundice the blood guanidine is increased Stimulated by Minot and Cutler's demonstration of the antagonistic action of calcium and guanidine in experimental carbon tetrachloride

and chloroform poisoning one of us (Moore) has treated a number of patients with post-arsphenamine jaundice with daily intravenous injections, each of 10 cc., of 10 per cent calcium gluconate The rate of symptomatic improvement seems more rapid than when calcium is omitted, and this form of treatment seems advisable in all instances of post-arsphenamine jaundice. For the past several years one of us (Kemp) has used intravenous glucose alone in the treatment of arsphenamine jaundice with very satisfactory results. Soffer, in a comprehensive review of all data concerning the treatment of post-arsphenamine jaundice, finds that a high carbohydrate diet is an extremely if not the most, important single therapeutic measure. He concludes

'Such diets should consist of 400 to 600 gm. of carbohydrate per day divided into five or six feedings.

'Those carbohydrate foods should be employed which are made up essentially of fructose and glucose, since these sugars are most readily converted into glycogen by the liver Thus, cane sugar which is hydrolyzed into glucose honey which is mostly glucose and fructose and fruit juices are most desirable.

'Where the amount of carbohydrate taken orally is inadequate, diets should be supplemented by a constant intravenous drip of 5 per cent glucose

'Insulin should be employed only when glycosuria is manifested.

'The use of cholagogues and choleretics in the treatment of arsphenamine jaundice is an unsound form of therapy

The conduct of further antisyphilitic treatment after post arsphenamine jaundice —This will depend largely on the stage of the patient's infection In any event, arsphenamine should be discontinued as soon as jaundice appears, not to be resumed until it has completely faded If the patient has early syphilis, treatment should not be interrupted, however and may be continued with bismuth and potassium iodide throughout the course of the complication. To let the patient go without any treatment may subject him to the danger and the physician to the embarrassment, of infectious relapse or neurorecurrence. If he has late syphilis, treatment may be suspended until the jaundice has cleared, to be resumed with a heavy metal. Three months or so after disappearance of the icterus, an arsphenamine may be resumed at first in minute dosage (0 05 gm.) increasing by similar small weekly increments until an average therapeutic dose is reached. This, as pointed out by Soffer is almost always perfectly tolerated. The rare instances of recurrence of jaundice (unless due to some entirely extraneous cause such as gall stones) call for complete abandonment of further efforts at arsphenamine therapy

The prognosis of post arsphenamine jaundice —O'Leary has recently provided the startling information that some of his patients with post-arsphenamine jaundice are returning to the clinic years later with outspoken cirrhosis of the liver We have been on the watch for a similar case but so far have not seen one. Clinically those of our own patients who have been followed over a period of years have remained quite well. In a recent exhaustive study of 24 patients followed from 2–20 years after

the development of post-arsphenamine jaundice Rankin and Marlow found that although there was laboratory evidence of mild residual liver damage in 18 of the 24 cases, in no instance did clinical evidence of cirrhosis subsequently develop In cases in which the original liver damage was severe or in those in which alcohol was a factor the residual liver dysfunction was greatly increased They point out that although arsphenamine is not contra-indicated in individuals who have developed jaundice while under treatment it must be given with caution particularly if there is evidence of severe liver damage at the time the jaundice first occurs. *This is in agreement with our clinical impression* and with the experiences of others.

Renal Injury from the Arsphenamines

As pointed out in Chapter VI, renal damage obvious from functional changes during life and from changes at necropsy may be produced in experimental animals with massive doses of the arsphenamines, but not with repeated small injections analogous in dosage to that used in man. Numerous studies of kidney function by means of dye excretion and blood chemical studies, in human patients undergoing arsphenamine therapy have shown no evidence of injury to the normal kidney Transitory albuminuria has been observed promptly clearing when the drug is withdrawn. We have administered the arsphenamines, especially neoarsphenamine *cautiously and in small doses (0 2–0 45 gm.) to patients* with pre-existing non-syphilitic nephritis, and have never seen any indication of further damage to the kidneys.

Nevertheless under certain circumstances, usually in association with post-arsenical dermatitis or as part of a blood dyscrasia there may be evidence of grave renal injury We have seen three patients with acute hemorrhagic nephritis following the use of sulpharsphenamine occurring independently of any other recognizable arsphenamine complication This, together with the known high incidence of dermatitis and blood dyscrasias, constitutes our reason for the abandonment of this drug in adults.

The inadvertent use of acid arsphenamine may be followed by a severe tubular nephritis with complete anuria.

All these renal reactions are fortunately very rare In actual practice renal damage *from the arsphenamines need not be feared.*

Reactions Produced by Tryparsamide

For many years following its introduction all workers were impressed by the lack of constitutional reactions following tryparsamide It was thought never to be responsible for the angioneurotic symptom complex and nitritoid reactions following its administration were almost unknown. During the past two or three years, however there has been a decided increase in the number of constitutional reactions to this drug In a review of the reactions following 43,308 injections given during the sixteen years from 1923 to 1939 Kopp and Solomon found that nitritoid reactions, which were practically unknown when tryparsamide was first introduced now occur in 8 6 per cent of patients In the majority of these patients this

reaction was preceded by other manifestations of idiosyncrasy particularly reactions of the gastro-intestinal type. In their series gastro-intestinal reactions similar to those following the arsphenamines occurred in 7.1 per cent of patients. This type of reaction has also increased recently. For the most part these gastro-intestinal reactions occur in patients who have received large amounts of tryparsamide continuously over a long period of time. In many the reaction recurred even with a decrease in dosage and contra-indicated the future use of the drug. This is in agreement with our recent experience. Kopp and Solomon also report the rare occurrence of convulsions, coma, and auditory and visual hallucinations following the administration of tryparsamide to patients with neurosyphilis. In most instances adequate preparation with the heavy metals and iodides prior to tryparsamide therapy prevents the occurrence of these reactions. There has apparently been no increase in the incidence of jaundice and dermatitis (Tables 19 and 22) but we have recently seen two patients develop severe exfoliative dermatitis following tryparsamide several months after their recovery from a similar episode caused by one of the arsphenamines. No instances of blood dyscrasias following tryparsamide have been reported.

The cause of the increased toxicity of tryparsamide is not known. Moore suggests that it may be due to undetected impurities of chemicals used in its manufacture and suggests that physicians report the type of reaction and the lot number of the drug causing it to the manufacturers. This will be of distinct help in aiding them to determine the cause of and eliminate these reactions.

Visual damage is the main complication of tryparsamide to be feared. Tryparsamide is closely related chemically to atoxyl and arsacetin and like these pentavalent arsenical drugs causes toxic phenomena largely centered in the central nervous system in experimental animals.

Sloan and Woods have studied the visual disturbance produced by tryparsamide among the Johns Hopkins cases and analyzed its occurrence among 2,087 cases of neurosyphilis without pre-existing optic nerve damage reported in the literature. One hundred seven (5.12 per cent) of the reported cases developed subjective reactions and 71 (3.4 per cent) objective reactions, the latter representing merely an advanced degree of damage to the optic nerve. The symptoms in both were identical.—from 6–24 hours after injection of tryparsamide, the patient complains of a 'dazzling' or 'shimmering' sensation or of a 'tremor in the air'. The sensation is described as similar to that produced by looking at snow in intense sunlight or at the hot air arising above an automobile radiator on a cold day. In dim illuminations, these symptoms disappear or are greatly diminished; in strong light they are increased. Their duration is inconstant, ranging from a few hours to several weeks. With this, there may be slight dimness or veiling of vision, the patient stating that in a dim light, objects appear gray.

In two-thirds of the patients with subjective reactions, ophthalmologic examination shows little or nothing. In the occasional case there is a low grade hyperemia of the fundus without blurring of the neuroretinal

margins or obscuration of the cup This is always indefinite and often disappears within 24 hours. The visual fields and blind spots are identical with those recorded before treatment. There are no scotomas, either absolute or relative.

The objective reactions to tryparsamide are classified by Sloan and Woods as acute and chronic. The acute type, which occurs rarely, is characterized by rapid loss of vision and results occasionally in complete and permanent blindness. In the majority of such patients, however, there is gradual improvement of vision and an increase in size of the visual fields.

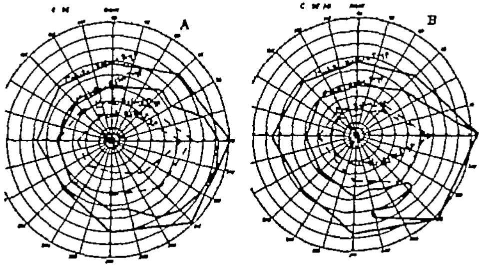


FIG. 12.—Typical fields showing slight contraction after chronic reaction to tryparsamide. (Sloan and Woods.)

In patients with the chronic type of reaction changes in the visual fields are the only characteristic finding, central visual acuity being undisturbed in the early stages of the reaction. Perimetry shows contraction of the form fields affecting particularly the nasal upper and lower fields, the temporal fields being involved last or not at all The color fields remain unaffected and there are no changes in the blind spots and no scotomas. In patients showing severe reactions, there is a reduction in the light sensitivity of the central retina. In moderate reactions the central light sense of the retina is as a rule unaffected though there may be reduction in sensitivity to light in the peripheral retina. In most of the severe cases, visual failure and field contraction slowly increase to a maximum within three weeks stopping, however well short of blindness *if the drug is discontinued* This constriction of the form fields tends to be permanent as indicated in Fig 13

Objective changes in the optic discs are delayed for several weeks or months after this length of time in the rare patients with permanent damage the nerve heads show the picture of papillomacular or even of primary atrophy The incidence of objective visual damage of this type

from tryparsamide is approximately 5 per cent of the patients treated

Factors influencing visual impairment from tryparsamide — The reaction tends to appear early in treatment, almost always before the fifth dose. If more than 16 injections are tolerated without reaction, its subsequent appearance need rarely be feared. There is no direct relationship to the dose of drug administered, provided a dose of 3 grams is not exceeded. Small doses as well as the average therapeutic dose may be responsible. *Visual impairment is especially prone to occur in patients with*

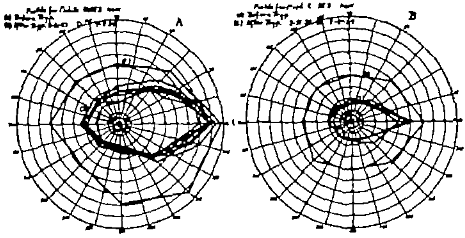


FIG. 13 —Stationary field defect after initial reaction to tryparsamide (Sloan and Woods.)

pre-existing damage to the optic nerve and is thus especially common in tabes or paresis.

The prevention and treatment of tryparsamide amblyopia — Before the commencement of tryparsamide therapy the patient's eyes should be carefully examined by a competent ophthalmologist.* Any organic defects, visual acuity with refraction correction, and especially visual fields are accurately recorded This examination serves as a baseline for future examinations if symptoms of visual damage occur If optic atrophy is present, the patient is not a suitable candidate for tryparsamide and should be treated by some other means. If the eyes are normal, treatment is started and the patient warned to report visual disturbances of any kind. If these occur the eyes are immediately re-examined. If no *changes in visual acuity or visual fields are noted use of the drug may be* cautiously continued by means of halving the usual dose and prolonging the interval between injections to two weeks.

* A recent decision of the Supreme Court of Appeals of Virginia, reported in the *Journal of the American Medical Association* (*Reed v Church*, 8 S.E [2d] 285 [Va. 1940]) affirms the medicolegal responsibility of the physician in the event of the development of tryparsamide amblyopia and concurs in the medical opinion that tryparsamide is "a potent drug which should be administered only under ocular (*sic*) control."

If, however any failure of central vision, and especially if any contraction of the visual fields is found *tryparsamide is immediately and permanently discontinued* By this means it is possible to employ the drug with relative safety and to reduce to a minimum damage to vision or to the nervous tissues of the eye.

Since such an important function as vision may be involved even slightly, the use of tryparsamide should be limited to the class of patients in whom the risk is justified by an appropriate therapeutic gain. So far as we now know tryparsamide is of value in no other conditions than trypanosomiasis and syphilis, and in the latter disease only when there is *involvement of the central nervous system. It should not be used in any* other circumstances.

The differentiation of optic atrophy due to tryparsamide from that caused by syphilis —Occasionally one is faced with the discovery of partial optic atrophy in a neurosyphilitic patient under treatment with tryparsamide in which there is doubt as to whether the atrophic process is due to the drug or the disease. This situation is particularly likely to arise if preliminary examination of the eyes prior to tryparsamide therapy has been omitted. The only differential diagnostic points are that (1) visual acuity *fields and fundi were known to be normal before treatment with* tryparsamide (2) the subjective complaint of blurred vision with accompanying constriction of the visual fields was known to occur suddenly and in direct relation to treatment with the drug (3) in atrophy due to the drug, central visual acuity is either undisturbed or usually returns promptly to its original level within a few weeks of the appearance of the reaction and remains normal in spite of slow progression of field constriction while in optic atrophy due to syphilis, loss of visual acuity and constriction of the fields usually go hand in hand (4) and most important, the field defects as a result of tryparsamide therapy are characteristic in that there is almost always sparing of the temporal field vertical constriction and never central scotoma, while in optic atrophy from syphilis the diminution of the visual fields is concentric and often with central scotoma.

Deaths from the arsenicals —Hahn in a study of our own material found the mortality rate of treatment with trivalent arsenicals to be 1 in 1,250 patients with one death to each 12,000 injections The mortality rate of treatment with bismuth was 1 in 19,550 patients with one death to 175 000 injections. No fatalities were attributable to tryparsamide In the period 1937–1940 4 800 patients received 64 000 injections of trivalent arsenical mostly mapharsen without fatality The mortality rate was 3 times as great in Negroes as in white patients and twice as great for females as for males The more frequent occurrence of acute yellow atrophy among *women accounted for the sex difference The mortality rate among* women was not influenced by pregnancy Amongst early syphilitics the mortality rate was only 1 to 2,800 treated patients Sixty per cent of 45 fatal reactions occurred in patients over 30 years of age and 50 per cent in patients with concomitant organic disease or toxic factors Acute yellow atrophy of the liver accounted for nearly 50 per cent of all fatalities derma

titis and the blood dyscrasias for 15 per cent each and hemorrhagic encephalitis for only 5 per cent. The remainder were due to a miscellaneous group of immediate as contrasted with delayed, arsenical reactions. All fatal reactions except blood dyscrasias tended to occur after 10 or less injections. Almost 50 per cent might have been prevented by consideration of the patient's physical condition and appropriate modification of therapy avoidance of technical errors, and prompt cessation of treatment with earliest signs of major intolerance. By this latter precaution, nearly all deaths due to blood dyscrasias could have been prevented. The most frequent anatomic findings were hepatic necrosis, dermatitis, hypoplasia of bone marrow and multiple hemorrhages.

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CHAPTER VIII

BISMUTH

BISMUTH was introduced into the treatment of syphilis in 1921 by Sazerac and Levaditi who developed the leads furnished by the unfinished experiments of Robert and Sauton The drug met with immediate acceptance, and in the past 20 years has almost completely replaced mercury in the treatment of early syphilis, and largely so in syphilis of all types. On the basis of clinical and experimental studies, bismuth appears to occupy a position in respect of therapeutic efficiency intermediate between that of arsphenamine and mercury

Bismuth preparations —The situation with reference to preparations of bismuth offered to the physician for clinical application is at present in a disgraceful state of chaos. The fact that the administration of this drug is not fraught with such disastrous possibilities of immediate toxic effects for the patient as is the use of arsenical compounds, has led to the preparation and advertisement for sale of almost every conceivable chemical compound of bismuth by pharmaceutical houses, each anxious to be represented by a bismuth product in its catalogue. No less than 113 different preparations available in Europe in 1928 are listed by Möller Many of these have been placed in the market before the performance of fundamental investigations of toxicity and therapeutic efficiency in animals and the physician who attempts to choose among them is lost in a confused mase of extravagant claims of superiority Fortunately in this country protection is afforded by the Council on Pharmacy and Chemistry of the American Medical Association, which will not accept any drug until it has been thoroughly studied in the laboratory In this chapter we shall consider only those preparations which have been accepted by the Council for admission to New and Non-Official Remedies. These are listed in Table 23 and the physician is strongly urged to select the preparation he prefers from them, or from among the products of other manufacturers, not listed in the table whose preparations are chemically identical with those described. There are, for example, several preparations of the alkaline tartrates or of bismuth subsalicylate which are equally acceptable with those of the designated manufacturers. Other products, until they or their chemical analogues have received the cachet of approval of the Council should not be employed

Classification of bismuth products on the basis of solubility — The first column of Table 23 separates the accepted bismuth products on the basis of their solubility a classification which is modified from that of Hanzlik and Mehrtens. Five compounds are insoluble in water and administered in oily suspension two are soluble in oil three are soluble in water and two in a special medium propylene glycol. These differences in solubility do not determine the route of administration since all are

Bismuth Products Accepted by the Council on Pharmacy and Chemistry of the American Medical Association Listed in New and Non-official Remedies

Classification	Trade name	Chemical name, vehicle of suspension or solution, and concentration	Approximate percentage content of metallic bismuth	Recommended dose (I.M.)	Manufacturer or Distributor
Insoluble, used in aqueous medium	None				
Insoluble used in oil	Bismuth subsalicylate	10 per cent suspension in peanut oil. Each cc. contains 0.13 gm. of drug	64 0	0 2 gm. (2 cc.) weekly	Parke Davis & Company
	Oleo-Bismuth	Bismuth oleate, suspended in olive oil. Each cc. equivalent of 0 05 gm. metallic bismuth	19 5	0 1 gm. (2cc.) once or twice weekly	Hoffman-LaRoche, Inc.
	Tartro-quiniobine	Suspension of quinine iodide 0 072 gm. and sodium potassium bismuth tartrate, 0 032 gm. in 1 cc. of oil	18–20	1–2 cc. weekly	Spicer & Company
	Mesurol	Basic bismuth methoxy hydroxy benzoate, 20 per cent suspension in sesame oil, each cc. equivalent of 0.11 gm metallic bismuth	54–57	0 2 gm. weekly	Winthrop Chemical Company Inc.
	Potassium bismuth tartrate	10 or 20 per cent suspension in almond oil, with 0.6 per cent butyn	56 0	0 2 gm (2 cc.) weekly	Abbott Laboratories
Soluble, used in oil	Bismo-cymol	Basic bismuth campho-carboxylate, 0 06 gm. in 1 cc.	37–38	0 1 gm. every 3–4 days	Abbott Laboratories
	Quiniobine	Quinine bismuth iodide rendered soluble in olive oil by means of lecithin. Each cc. contains 0 05 gm. bismuth, 0.03 gm. quinine, 0.075 gm. iodine, and 0.22 gm. lecithin	18–20	1–2 cc. twice weekly	Spicer and Company

TABLE 23 (*Continued*)

Classification	Trade name	Chemical name, vehicle of suspension or solution, and concentration	Approximate percentage content of metallic bismuth	Recommended dose (I M.)	Manufacturer or Distributor
Soluble, used in oil (*Cont.*)	Bilipoeol	Alpha-carboxethyl-beta-methyl-nonoate of bismuth, dissolved in olive oil, each cc. containing 0 04 gm. metallic bismuth	45	2.0 cc. twice to three times weekly	Ulmer Laboratories
Soluble, used in aqueous medium	Bismosol	Potassium sodium bismuth tartrate in 10 per cent glucose solution, 0.1 gm. in 1 cc.	41 0	0 1 gm (1 cc.) twice weekly	Merck and Company
	Bismuth sodium tartrate	0.03 gm. drug and 0.04 gm benzyl alcohol in 2 cc. 50 per cent sucrose solution	73 8	0 03 gm. 2–3 times weekly	G D Searle & Company
	Thio-bismol	Bismuth thioglycollate, 0.2 gm. in 1 cc. of distilled water	37 8	0 2 gm. (1 cc.) twice weekly	Parke Davis & Company
Soluble in propylene glycol	Iodobismitol	Sodium iodobismuthite, dissolved in propylene glycol (0.057 to 0 066 gm. per cc.)	31 5	2 cc. every 2–3 days	E. R. Squibb & Sons
	Sobisminol	Chemical nature not yet fully established. Each cc. contains 20 mgms. bismuth in an aqueous solution, 50 per cent propylene glycol and an organic *bismuth compound*	19 5 to 20 25	1–2 cc. twice weekly	Eli Lilly & Co E. R. Squibb & *Sons; Cutter* Laboratories
Insoluble in all ordinary and special solvents	None				
For oral use	Sobisminol mass	Chemical nature not yet fully established. Each capsule represents 150 mgms. metallic bismuth		2–3 capsules 3 times daily	Eli Lilly & Co E. R. Squibb & Sons Cutter Laboratories

In this column dosage is expressed in terms of the drug mentioned. It only adds to the general confusion to express it in terms of metallic bismuth. Lomholt suggests, however that adequate dosage is 0.5 mg per kilo per week of metallic bismuth. This implies, of course, that the bismuth content of the drug employed is definitely known

given intramuscularly They do however materially affect absorption and excretion, factors on which great stress has recently been laid as indicating the desirability of one or another product.*

The relative toxicity of bismuth products by various routes of administration.—Early studies on bismuth compounds showed that all of them were much more toxic when given intravenously than intramuscularly This has been repeatedly confirmed by various observers, and is apparently true of all products now in common use except the thioglycollate. The variation in toxicity is probably a direct expression of rapidity of absorption. The minimum lethal dose for experimental animals by the intramuscular route is from 4–200 times greater than by the intravenous route. These data for certain of the commoner soluble preparations used in the United States are found in Table 24

TABLE 24

RELATIVE TOXICITY IN EXPERIMENTAL ANIMALS OF INTRAVENOUS AND INTRAMUSCULAR ADMINISTRATION OF SOLUBLE BISMUTH PRODUCTS

Drug	Lethal or tolerated single dose in mg/kg when given	
	I V	I M.
Potassium bismuth tartrate	8–15	300
Bismuth sodium tartrate	15	250–600
Sodium potassium bismuth tartrate	20–50	200–800
Sodium iodobismuthite	30–60	120–130
Bismuth thioglycollate	15	24

There have been several reported deaths in human beings from the intravenous administration of bismuth salts. For the time being, therefore and unless and until newer compounds are developed in which the margin of safety is greater none of the currently available bismuth preparations should be administered intravenously the intramuscular route should always be used.

Absorption and excretion of bismuth in experimental animals and man.—Elaborate studies of bismuth absorption and excretion have been carried out by numerous investigators, prominent among whom are Lomholt, Levaditi and his associates, Gruhzit, Kolle, von Oettingen, Handik and Mehrtens, Kolmer and particularly Sollmann, Cole, and

* Handik and Mehrtens lay considerable stress on the penetrability of iodobismitol into the nervous system, as judged by its appearance in the spinal fluid, an observation not confirmed by Klauder and Brown, or by Sézary and his co-workers. As already pointed out in the discussion on the arsphenamines, the mere fact of the presence of drug in the cerebrospinal fluid does not necessarily imply its value in neurosyphilis. As a matter of fact, there is as yet no evidence that bismuth therapy in neurosyphilis accomplishes any more than in any other type of syphilitic infection, or as much as the arsenicals and certainly we have not as yet reached the point of refinement which enables us to choose a particular bismuth product for a particular type of syphilis.

route, the curative dose in experimental rabbits by either route was almost identical (see Table 25) As a result of these experiments, Kolle drew the conclusion, generally accepted until recently that bismuth salts used in the treatment of syphilis were not actively treponemicidal but treponemostatic that is, they inhibited the multiplication of the treponemes without destroying them A third group of observers, notably Stokes, have credited the therapeutic effect of bismuth to its supposed resistance building power and have suggested that its main use in syphilis is to stimulate the defense mechanism of the host. This is pure assumption since there is no satisfactory evidence either clinical or experimental that it is possible artificially to enhance resistance to syphilis by bismuth or any other drug

The exact mechanism of the action of bismuth compounds in the treatment of syphilis has been recently explained by Eagle. In a series of well controlled experiments he has shown that the soluble bismuth salts are treponemicidal *in vitro* in dilutions of 1–60 000 to 1–225 000 i.e in dilutions approximating closely their concentration in the body fluids following the usual therapeutic doses. Eagle has shown further that tissue extracts do not contribute to the therapeutic action of bismuth compounds. On the contrary they caused a marked decrease in the treponemicidal activity of each of the bismuth preparations he studied. As with the arsphenamines, Eagle believes that the treponemicidal activity of bismuth compounds is due to their affinity for the sulphydryl group in the *Treponema pallidum* (p. 72) Although Eagle's experiments are concerned only with soluble bismuth preparations, there is no reason to believe that the insoluble salts do not act in a similar manner

The choice of a soluble versus an insoluble bismuth preparation —The factors which decide the choice of a bismuth preparation are the rates of absorption and excretion toxicity and therapeutic efficiency As pointed out by Kolmer these factors depend upon the ease and rapidity with which the various bismuth salts are dissociated in the body into elemental bismuth A preparation which furnishes a more or less continuous daily excretion of 2-4 mgms of bismuth is according to Cole potentially a satisfactory antisyphilitic agent. This effect may be obtained readily with less inconvenience and expense and without danger to the patient by *the intramuscular injection of insoluble salts. In rare cases in* which it is inadvisable to start treatment with arsphenamines and yet in which a prompt therapeutic effect is desired, a soluble preparation may be used for the first two or three weeks of treatment The rapid excretion of these latter compounds necessitates their administration twice to three times weekly depending upon the preparation used This not only adds to the expense of treatment but materially to the inconvenience and sometimes to the discomfort of the patient. This would not be a drawback if the therapeutic advantage gained were commensurate with the added expenditure of time and money We know of no evidence that in the long run soluble bismuth preparations will do any more than insoluble compounds. As soon as the desired effect of the administration of the soluble salts has been obtained, insoluble salts should be substituted for them.

An effect midway between the soluble and the insoluble compounds is obtained by use of the oil soluble preparations. We have had very little experience with them but we know of no particular advantage to be gained from their use.

From the above it is obvious that we recommend the insoluble bismuth preparations for routine use With the average therapeutic dose, toxic manifestations are no more common with insoluble than with soluble preparations and in spite of the theoretical suggestion there appears clinically to be no risk of storage of dangerous amounts of bismuth in the body In addition, these preparations are for the most part inexpensive, are painless and require administration only once weekly Of the insoluble salts we have used only the subsalicylate, oleate, and tartrate. In our experience, and in the experiences of Irgang and his collaborators and Kolmer and his, the subsalicylate is therapeutically more active and less toxic than any of the others causes less local pain, and is absorbed almost as rapidly as the insoluble tartrate. We therefore advise the practitioner to limit himself largely to its use. It must be remembered that the preparations of different manufacturers may differ widely with regard to local reactions. This seems to depend upon the oil in which the drug is suspended (peanut oil is less irritating than other vegetable oils) As second choice we prefer the oleate, and last of all the tartrate because of its tendency to produce local reactions.

Although all the bismuth preparations listed in New and Non-Official Remedies are therapeutically active, Cole suggests that the physician take his choice from the following For rapid effect, sodium bismuth tartrate in water sobisminol or iodobismitol. These preparations must be given 2–3 times a week. For moderate bismuth effect, bilipsol or bismocymol. These preparations must be injected every 5–7 days. For a slow sustained effect, sodium bismuth tartrate or bismuth subsalicylate injections of which are given once weekly It must be remembered that none of these preparations are to be given intravenously

The therapeutic efficiency of bismuth in experimental and human syphilis—Something has already been said as to these points. All the bismuth preparations listed will heal lesions and cause the disappearance of surface organisms in both rabbits and human beings. Both of these results are more slowly obtained than with the arsphenamines lesions heal in weeks rather than in days organisms disappear in days rather than in hours. Both effects are, however produced much more quickly and surely than with mercury Experimental rabbit syphilis is apparently curable, in the sense of freedom from relapse and negative lymph node transfers, with either single large or repeated smaller doses of bismuth and especially when the drug is given intramuscularly this may be accomplished with doses far below the maximum tolerated or minimal lethal dose. The therapeutic index of some of the bismuth preparations listed in New and Non-Official Remedies, as determined by Kolmer and his colleagues, is given in Table 26. As shown in this table it varies from 1 for the water soluble thiobisminol to 166 for the insoluble bismuth subsalicylate. However (and here is another fundamental dif

ference between bismuth and arsphenamine preparations), none of the bismuth compounds so far studied (except those in chemical combination with an arsphenamine, such as bismarsen) have any noteworthy trypanocidal effect.

The effect of bismuth on the serologic tests in early syphilis has been studied by many observers, particularly in France. In this country the most elaborate study is by Irgang and his associates, who treated a large group of patients with early secondary syphilis with 20 injections each of

TABLE 26

CHEMOTHERAPEUTIC INDEX OF VARIOUS BISMUTH COMPOUNDS
(From Kolmer Brown and Rule)

Compounds	Preparation	Per cent elemental Bi	Approximate maximum tolerated dose per kilogram (gm. of elemental Bi)	Approximate minimal curative dose per kilogram (gm. elemental Bi)	Indices
Potassium bismuth tartrate	Aqueous	64	0 256	0 00384	67
Bismuth sodium tartrate	Aqueous	73	0 292	0 00438	65
Thio-bismol	Aqueous	38	0 0076	0 0076	1
Bismosol	Aqueous	35	0 0175	0 0035	5
Iodobismitol	Propylene glycol	21	0 105	0 0021	50
Bilipsol	Oil solution	45	0 200	0 0027	110
Bismo-cymol	Oil solution	39	0 312	0 0039	80
Potassium bismuth tartrate	Oil suspension	64	0 384	0 00384	100
Bismuth subsalicylate	Oil suspension	58	0 464	0 00348	133
Bismuth subsalicylate	Oil suspension	58	0 580	0 00348	166
Bismuth salicylate	Oil suspension	58	0 464	0 00348	133
Mesurol	Oil suspension	56	0 560	0 0036	166
Oleo-bi Roche	Oil suspension	20	0 160	0 0120	13

one of several bismuth preparations. Their effect upon reversal of the blood serologic test (Wassermann) is shown in Table 27. As shown in this table, the insoluble bismuth subsalicylate was most efficient, followed in turn by bismocymol bismuth sodium tartrate, quinine bismuth iodide and tartro-quiniobine. The least effective was bismuth tartrate administered intravenously. In spite of the favorable showing of some of these bismuth salts, the results as to serologic reversal are far inferior to those following the administration of the arsphenamines (see Fig. 9). We make no comment on the effect of bismuth on serologic tests in late syphilis since the material in this monograph makes it evident that we lay comparatively little stress on such a study.

There are few reliable data on the ultimate clinical outcome in patients with early syphilis treated with bismuth alone for comparison with

arsphenamine statistics. Nowhere except in France, so far as we know, has anyone had the temerity to omit the arsphenamines in early syphilis in favor of bismuth In France this has been done by a number of clinicians whose reports do not lend themselves to statistical treatment. It seems clear however, that infectious clinical relapse, and serologic relapse also are more common in patients treated with bismuth alone than in those who also receive arsenical therapy and as a matter of fact, this has been used as an explanation for the fact that the general incidence of syphilis seems to have been rising in France in recent years, while falling in the rest of Europe

The treatment of syphilis by bismuth preparations administered orally—Bismuth was first used orally in the treatment of experimental rabbit syphilis by Sazerac and Levaditi in 1921 They thought

TABLE 27

THE EFFECT OF VARIOUS BISMUTH COMPOUNDS ON THE BLOOD WASSERMANN IN EARLY SYPHILIS

(From Irgang, Alexander and Sala)

	Cases	Negative reactions	
		Number	Per cent
Bismuth salicylate in oily suspension	21	17	80 9
Bismo-cymol	19	13	68
Bismuth sodium tartrate	19	12	63
Quinine bismuth iodide	19	12	63
Tartro-quinobine	14	8	57
Bismuth tartrate intravenously	7	0	0

the drug by this route had promise but made no further experimental studies. A short time later Fournier and Guénot used sodium and potassium tartrobismuthate one of the preparations studied experimentally by Levaditi in the treatment of human syphilis, and discarded it as worthless. In 1935 Kolmer reported favorable results in rabbit syphilis from the oral administration of potassium tartrobismuthate. Almost simultaneously Serefis and Mulzer reported the successful treatment of both experimental and human syphilis with a complex amino acid bismuth salt of oxytricarballylic acid known commercially as bismutrat. Experimental studies by Rein and Sulzberger Kemp and Rosahn, Clarke and Marsh, and by Thomas failed to confirm the claims made by Kolmer and by Serefis and Mulzer

In 1937 Hanzlik and his co-workers introduced sodium bismuthate called sobisminol a preparation which they thought beneficial when administered either orally or intramuscularly in experimental rabbit syphilis This drug has been the subject of extensive study by Hanzlik and his co-workers and by Sollmann and his. As judged by experimental and clinical studies of the urinary excretion of bismuth it is absorbed satisfactorily from the gastro-intestinal tract and gives a sustained urine bismuth level beginning the day following its administration and reaching

a peak on about the fourth day The claims for its value in experimental rabbit syphilis have not been confirmed (Shaw and Kemp, and Clarke) Nevertheless, it has been used successfully in the treatment of human syphilis by Meininger and Barnett and by Scholtz McEachern and Wood. These workers found that it produced rapid involution of the lesions of early syphilis with the disappearance of treponemes. It also proved efficacious in the treatment of benign late syphilis The drug has been recently accepted by the Council on Pharmacy and Chemistry for both oral and intramuscular administration (see Table 23) It is given in capsule form, each one representing 150 mgms. of metallic bismuth. The dosage is 4–6 capsules daily It must be remembered that sobisminol mass, as the preparation for oral administration is known cannot be recommended as a substitute for the present drugs used intramuscularly in the treatment of syphilis. It is to be used only in cases where intramuscular injections of bismuth are contra-indicated or impossible to obtain. It is not advisable, except under most unusual circumstances, to substitute sobisminol mass for other bismuth preparations in the treatment of early syphilis.

The chief objection to the oral treatment of syphilis with bismuth or any other compound is that only exceptionally intelligent and cooperative patients can be trusted to carry out the necessary long continued self administration of the drug Obviously considering the population groups in which the disease is most prevalent, this consideration sharply limits the usefulness of oral treatment.

The efficiency of bismuth as compared with arsphenamine and mercury.—It will be apparent from what has been said that bismuth cannot replace the arsenical drugs in the treatment of syphilis. Where maximum treponemicidal effect is desired and especially in early syphilis, the arsenicals must be used. The possible treponemistatic effect of bismuth makes it an ideal adjuvant for arsenic in the intervals between arsenical courses it may hold in check the organisms not destroyed by the arsenical drug perhaps destroying more either by virtue of its own comparatively weak treponemicidal action or by permitting the action of the body's own defense mechanism. The only circumstances under which bismuth should form the sole reliance of treatment are first, in those patients whose general physical condition contra-indicates the use of the more active and more toxic arsenicals, as, for example, certain patients with cardiovascular syphilis and second, those who have undergone such a serious arsenical reaction as to preclude the further use of arsenic, as, for example, exfoliative dermatitis.

As for a comparison of bismuth and mercury this must at present rest on the evidence of animal experimentation and in human beings, on the relative effects of the drugs on healing of lesions disappearance of surface organisms and the reversal of the blood serologic test. A comparison on the basis of ultimate clinical outcome is difficult to make because in both instances the evaluation of results is complicated by the universal use of the arsphenamines and because also bismuth has not been in use for a long enough period of time to justify accurate conclusions. Certain data in early syphilis are available, from the study of the C.C G these are

presented in Chapter XIII. These indicate the superiority of bismuth over mercury and, in addition to definite statistical information, the clinical impressions of many observers the world over, in which we share, so clearly establish this fact that in most large clinics bismuth has almost completely replaced the older drug in all types of syphilitic infection.

The local tissue damage produced by the injection of bismuth —Gruhzit has studied histologically the tissue damage produced by the intramuscular injection of bismuth compounds. With each compound tested there was definite injury, least in the case of the thioglycollate, most marked with the tartrate. There is local necrosis of muscle fibers which is only slowly absorbed and replaced by scar tissue. With some compounds, small sterile abscesses were formed. These changes, demonstrable in experimental animals, are not, however a serious drawback to the use of bismuth in human beings. The gluteal muscle mass is sufficiently large to tolerate 50–100 or more injections without serious difficulty and with much less evidence of destruction of muscle fibres and subsequent scarring than from the use of mercury preparations.

The general histologic changes produced by bismuth —In animals poisoned by single large doses of bismuth compounds, the chief pathological changes are in the kidney and liver with little or no significant alteration to other organs. There is a marked tubular nephrosis, with severe degenerative changes resembling those produced by mercury poisoning. Lesions in the liver are less prominent, but consist of cloudy swelling and central necrosis. These alterations have been observed with all the bismuth compounds studied. They are much more frequent after the intravenous than after the intramuscular administration of these drugs, and severe changes may be produced by the repeated intravenous injection of relatively small doses. However in animals treated with repeated intramuscular injections in a dosage analogous to the average therapeutic dose in man, pathologic damage to any organs is conspicuous by its absence.

The toxic effects of bismuth observed clinically —The literature on the reactions produced by bismuth has been thoroughly reviewed by Julinsberg. He points out that the incidence and severity of toxic manifestations depend on the mode of administration (for which reason the intravenous route is barred) on the frequency of injection and the size of the dose, and (as to local reactions) on the vehicle used.

Local reactions Pain.—The intramuscular injection of most bismuth products soluble or insoluble, is less painful than that of mercury salts. There is some variation among bismuth preparations. We have had little experience with water or oil-soluble preparations iodobismitol in propylene glycol is so painful as not to be tolerated by many patients. Of the insoluble salts, the tartrate is most, the oleate and subsalicylate, least painful. This seems to depend at least partly on the vehicle of suspension. The subsalicylate in olive oil for example, causes so much pain as to evoke loud protests from patients in peanut oil it is bland and non-irritating. The explanation for this is not clear We have never been able to see any advantage to adding an anesthetic such as butyn to the preparation. The

effect of this wears off in an hour or so, and patients object not to the immediate pain of injection but to the after soreness lasting several days.

With all preparations pain may be decreased by correct technique of injection (see Chapter XI) and by massage of the buttock for 2–5 minutes after injection. This also distributes the injected drug and aids in absorption

Sterile abscesses after bismuth are very rare. In our experience covering more than 200 000 injections, we have seen only seven five of which occurred after the campho-carboxylate. For this reason, the use of this particular product is not advised. *Should such an accident occur it is* best treated not by incision and drainage the wound of which may take a long time to heal but by multiple aspiration, repeated if necessary, through a large bore needle.

Accidental intravascular injection Oil embolism bismuth poisoning.—Owing to the greatly increased toxicity of bismuth when given into the blood stream great care must be taken during injection to avoid injecting the drug into a blood vessel This is best accomplished first, by using a large needle, at least 19 gauge second, by introducing the needle alone and dry i e, with no drug in its bore and without the syringe attached so that blood will appear promptly if a vessel is struck third by aspiration for at least 10 seconds after the syringe is attached. Failure to observe these precautions may lead to disaster, the nature of which *depends on whether the blood vessel entered is a vein or an artery*

If a vein is injected with an oil-suspended insoluble bismuth preparation the immediate effect is oil embolism, manifested clinically by tightness in the chest and uncontrollable coughing, sometimes with grave shock as a result of the deposit of oil emboli in the lung capillaries. The secondary effect may be the rapid onset of grave symptoms of bismuth intoxication as the result of rapid absorption of bismuth from multiple emboli in the tissues. One such case has occurred in our own clinic, with an extensive hemorrhagic and necrotic skin eruption, stomatitis nephritis, bronchopneumonia and death If this accident occurs, treatment is symptomatic only

Arterial embolism.—If an artery is entered the patient may be spared the danger of generalised bismuth poisoning but the injected bismuth *mass is distributed as multiple emboli to the smaller arterioles* supplying the buttock. This is manifested by immediate severe local pain ischemia appearing within a few hours a localised hemorrhagic skin eruption appearing within 24 hours in the distribution of the smaller arterioles of the skin and creating a racemose pattern similar to that seen in cutis marmorata (marbled skin) or in the pigmentation of 'toasted shins' a marked painful induration of the buttock and finally in some instances central necrosis and sloughing with very slow healing Fortunately arterial embolism is a very rare accident. It has been particularly stressed in this country by Gammel who has seen three examples. We have observed it only once. It is usually unavoidable in that a return flow of blood through the needle when introduced or on aspiration may not be present. The only treatment consists of rest, hot applications and, in more

serious cases, surgical removal of the gangrenous area with subsequent skin grafting

Sclerosing myositis of the buttock with atrophy of the glutei muscles and their partial replacement by dense connective tissue scar is much less a feature after repeated bismuth injections than after mercury We have seen many patients who have received 50 or more injections of bismuth without such difficulty In the occasional case it may occur necessitating the abandonment of intramuscular therapy

General reactions Oral cavity Bismuth pigmentation—Very early in the use of bismuth it was noted that effects were produced in the mouth intermediate between those caused by lead and mercury In practically all patients receiving more than a half dozen injections of bismuth a bluish gray pigmented line will appear at the gum margins almost identical with but without the grave significance of the lead line of lead poisoning. Generally as more bismuth is given (almost always after as much as 24 doses) this bluish pigmentation involves not only the gum margins but the buccal surfaces as well, and particularly the soft palate and velum and the inner surfaces of the cheeks Over the palate it is usually diffuse over the cheeks patchy Once having occurred it may persist for years, with only gradual fading and unimproved by efforts to remove it, such as sodium thiosulphate intravenously It is due to the actual impregnation with bismuth (sulphide?) of the endothelial and fibrous tissue cells of the summits of the papillae. It is objectionable for cosmetic and aesthetic reasons, especially in young women. It is called to the attention of many patients by their dentists, who not knowing that the patient is receiving antisyphilitic treatment, suspect lead poisoning This pigmentation carries with it no serious significance for the patient s general health though most authors feel that if it is extensive bismuth therapy should be interrupted. Our personal feeling is that it is a necessary concomitant of adequate bismuth therapy and indeed that its absence serves as an index of inadequate dosage. It need not be allowed to interfere with subsequent treatment which seems desirable for the patient's ultimate health provided it is not associated with other symptoms of toxicity

Stomatitis—Fortunately ulcerative stomatitis is much less frequent after bismuth than after mercury though it may occur It is definitely associated with the oral hygiene of the patient, i.e. commoner in individuals with an already existing gingivitis, especially if Vincent s organisms are present and with the frequency of administration and size of the dose of the drug In our own clinic, stomatitis is practically unknown on a weekly dosage of 0.2 gram of the subsalicylate but during a period when this dosage was increased to 0.26 gram per week, it occurred with considerable frequency As in mercurial stomatitis, secondary Vincent s infection of the ulcerated areas usually occurs. Treatment of the local lesion consists of arsphenamine powder or solution, or of 5 per cent solution of chromic acid locally (if Vincent s infection is present) sodium perborate mouth wash, and immediate cessation of bismuth therapy Severe bismuth stomatitis is often associated with nephrosis (cf p 149)

The ideal for patients undergoing bismuth treatment is, of course, pre-

liminary dental prophylaxis and constant attention to oral hygiene with the use of potassium chlorate toothpaste or mouthwash. In actual practice, however, this is rarely attainable in most individuals, and one must accept the small risk that stomatitis will occur. We know of no definite evidence that dietary modifications will influence the appearance of stomatitis in the slightest, and see no reason for insisting upon them.

Effect of bismuth on stomach and intestines.—Enteritis with bloody diarrhea is also far less common after bismuth than after mercury. Cases have been reported, but none has occurred in our clinic. Also very rarely there may be anorexia, nausea and vomiting, and simple diarrhea. Generally speaking, however, the drug causes no noticeable disturbance of gastro-intestinal function.

Effect of bismuth on the liver.—As already pointed out, cloudy swelling and central necrosis of the liver may be produced in experimental animals with toxic doses of bismuth, and the drug may be demonstrated in the tissues of this organ. In therapeutic doses these changes are absent and little is known of the effect of the small doses usually employed in man. Occasionally slight to moderate jaundice of the obstructive type with enlargement of the liver, acholic stools and bile in the urine has been observed in the midst of or after bismuth therapy. We have seen *only 2 such occurrences, however, unless the patient had previously received* an arsphenamine, and in most cases it has been frankly puzzling to determine whether the jaundice was due to arsphenamine or bismuth or was simply catarrhal in nature. In any event, the liver damage is not permanent, and more bismuth may be given subsequently without fear of repetition of the jaundice.

Effect of bismuth on the kidneys.—Particular interest attaches to the effect of bismuth on the kidneys and on renal function. Like certain of the mercurial drugs, bismuth exercises a mild diuretic effect, but this is not as marked as with salyrgan, for example, and bismuth has not come into general use as a diuretic in dropsical conditions.

In experimental animals poisoned with large doses of bismuth a tubular nephrosis is found which does not, however, occur when repeated small doses of therapeutic size are given. Albuminuria and cylindruria have been occasionally observed in patients undergoing treatment with bismuth, but much less frequently and usually to a much less extent than after mercury. There are so far no reported instances of serious permanent damage to the kidneys. Alterations in renal function (phthalein output, blood chemistry, etc.) have been looked for in bismuth treated patients, but have not been found. It is even possible to administer the drug in small doses to patients with an already existing nephritis without causing any evidence of increased renal injury. There is also no evidence of cumulative toxic effect on the kidney when the drug is repeatedly administered over long periods of time. *In general it may be said that during bismuth therapy* the same precautions should be observed as during arsphenamine treatment: examination of the urine at fairly frequent intervals with temporary cessation of therapy if albumin or casts appear. In almost all such cases,

the evidences of renal irritation are only transient and subsequent treatment may be cautiously but safely undertaken.

Exceptions to these statements are found in patients with severe ulcerative bismuth stomatitis, in whom the characteristic clinical and chemical findings of tubular nephrosis may also occur We have seen a half dozen such patients, one or two of whom were seriously ill All recovered promptly however, without apparent residual renal damage.

Skin eruptions from bismuth —These are relatively rare and of little practical significance. Pruritis, urticaria, lichenoid eruptions, erythematous rashes with miliaria-like vesiculation, desquamative erythrodermia, exfoliative dermatitis and purpura have all been described. We have seen only two patients in whom a skin rash could be definitely ascribed to bismuth. One of these was the patient already mentioned who developed a hemorrhagic gangrenous eruption associated with stomatitis, nephritis and broncho-pneumonia, after the accidental intravenous injection of the drug. The other was similar but fortunately much milder Cutaneous reactions are said to depend on the susceptibility of the patient rather than on the size of the dose. It is generally advised that should such a reaction occur, bismuth therapy be permanently abandoned.

Argyria —A curious phenomenon more fully described in the chapter on arsenical reactions, is the association of bismuth with silver arsphenamine in the production of argyria. This is not to be feared until a large quantity of both drugs—at least 24 injections of each—has been given. It is associated with extensive bismuth pigmentation of the buccal mucosa, and once having occurred, is permanent. Six such patients have been observed in our material.

Effect of bismuth on the blood —The phenomenon of grave secondary anemia associated with basophilic stippling of the red cells, so frequent after lead has not been observed as a result of bismuth A mild secondary anemia is said sometimes to occur but we have never seen a patient in whom this association was definite.

Peripheral neuritis —This, another common manifestation of lead poisoning, is also very rare after bismuth, though we have seen two patients in whom the drug could apparently be incriminated. It is usually mild and disappears promptly on withdrawal of the drug, and the parenteral administration of large doses of thiamin chloride (cf p 111)

Unexplained phenomena Bismuth arthralgia —In a rare patient, each injection of bismuth is followed by generalized malaise slight fever, and grippe-like aching of the bones and joints. The cause of this is unknown It is thought to be due to individual hypersusceptibility Once or twice in our experience it has been severe enough to necessitate the substitution of mercury for bismuth.

The treatment of bismuth intoxication by Aub s method of treating lead poisoning —The similarity of certain features of lead and bismuth poisoning would make it seem worthwhile to try in the one the methods of treatment elaborated by Aub and his co-workers for the other To paraphrase During severe intoxication it is apparently wiser

to facilitate *storage* of bismuth by ingestion of ample calcium rather than to set it free After the acute toxic episodes have passed, *elimination* of bismuth may be accelerated by a low calcium intake, acids and their ammonium salts, sodium bicarbonate and potassium iodide Caution should be exercised in using these forms of treatment on patients with nephritis.

This method of treatment, proved to be of great value in lead poisoning, has not been used, so far as we know in patients with severe bismuth intoxication. Hanzlik and Mehrtens in some incomplete experiments question the value of the method in aiding the excretion of bismuth, which they feel is best enhanced by copious water and sodium chloride intake.

Herxheimer reaction from bismuth —There have been a few reported cases of observed Herxheimer effect—intensification of syphilitic lesions, therapeutic shock—after bismuth Practically all however have been in skin lesions only and all have been very mild. The treponemicidal action of bismuth is so slow, as compared to that of arsphenamine, that *a priori* one would expect the Herxheimer reaction to be absent or minimal As a matter of fact, it is not observed in those types of late syphilis (gumma of the larynx, cardiovascular or neurosyphilis) in which it forms so prominent a feature of arsenical therapy and under these circumstances the initiation of treatment with bismuth is not only feasible but advisable.

Summary of the toxic effects of bismuth —In general it may be said that except for bluish pigmentation of the gums and buccal mucosa, the administration of bismuth in average therapeutic doses at weekly intervals is remarkably free of any toxic manifestations, as compared with arsphenamine or mercury Periods of bismuth therapy often come to the patient as a grateful relief from treatment discomforts. He learns that he may eat as usual and that reactions are not to be anticipated. From the purely clinical standpoint, the fears of experimental investigators that repeated injections of insoluble salts slowly absorbed at irregular rates over very long periods of time would be responsible for a greatly increased incidence of serious bismuth reactions have not been realized. We have given as many as 100 injections of bismuth subsalicylate, totalling 20 grams of the drug to a single patient in divided courses over a period of 2–3 years without the slightest evidence of bismuth intoxication.

Deaths from bismuth —In rare instances (35 instances since 1922 collected by Beerman) death may result from treatment with bismuth. It is usually due to the accidental intravenous injection of the drug.

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tively to the deposition of mercury sulphide in dental pockets where hydrogen sulphide is formed by the action of putrefactive bacteria. The insoluble sulphide causes local tissue necrosis, and this in turn is secondarily invaded by the pathogenic flora of the mouth especially Vincent's spirillae and fusiform bacilli, with the production of a severe ulcerative stomatitis. There is however no visible pigmented line at the gum margins such as is caused by bismuth The stomatitis is usually preceded by halitosis, soreness of the gums, aching of the teeth and excessive salivation

Treatment of the reaction consists first in immediate cessation of mercurial therapy though this is difficult if intramuscular injections of an insoluble salt have been given. (We have seen such severe stomatitides after the injection of mercury salicylate and of grey oil that we are firmly opposed to this method of treatment.) If Vincent's organisms are present, dusting with arsphenamine powder or painting with a 5 per cent chromic acid or 1–100 arsphenamine solution will aid in healing A potassium chlorate mouth wash (2 per cent) is helpful as is one of 1–4000 potassium permanganate. Severe cases should be placed in bed. Sodium thiosulphate, suggested by Dennie and McBride, is in our opinion of no value (for further details, see Chapter VII)

Dental prophylaxis before mercurial treatment will do much to avoid the appearance of stomatitis. For patients under treatment, a potassium chlorate toothpaste and mouthwash are also helpful. We are not persuaded that smoking or abstinence from it plays any rôle. It need hardly be said that the desideratum during mercurial therapy is not to produce salivation or stomatitis but to avoid it.

Gastro-intestinal disturbances —When mercury is administered by mouth in any form, anorexia, mild gastric distress, occasionally nausea and diarrhea, are prone to occur This feature, added to the relative therapeutic inefficacy of this method of giving the drug has led to the practical abandonment of mouth medication Certain patients seem unusually susceptible to the drug by any route and promptly develop diarrhea, the stools often containing blood and mucus, together with mild or severe abdominal cramps. Under these circumstances the drug should be discontinued at once, and the diarrhea treated symptomatically with bland diet, rest, paregoric (4 cc. every 4 hours) and bismuth subcarbonate (1–2 gms. every 2–3 hours)

Renal damage —Even small amounts of mercury may produce significant tubular damage in experimental animals. In man, average therapeutic dosage especially when the drug is given by inunction is rarely provocative of a grave nephrosis. Albuminuria and moderate cylindruria may occur and should be watched for by tests of the urine repeated from time to time. If they appear discontinuance of mercury and the temporary substitution of the less toxic bismuth or arsenical preparations is indicated. Personally we have seen no instance of serious and permanent renal damage which could be definitely and directly attributed to the therapeutic use of mercury but such cases have been reported Perhaps the relative immunity of our own clinic from such accidents is due to the

have pointed out in Chapter VIII there is no satisfactory evidence that mercury or any other drug is capable of stimulating the production of antibodies to the treponeme. The hypothesis therefore that mercury is a 'resistance builder' is not supported by any known fact.

The absorption and excretion of mercury.—Mercury may be absorbed through the gastro-intestinal tract skin lungs or after intravenous or intramuscular injection. The rate and degree of excretion depend on the route of administration and the solubility of the compound employed. Speaking generally, most of the drug (⅓ to ½ or more) is eliminated by the kidneys, most of the remainder in the feces and small quantities in saliva and sweat. The appearance of mercury in the urine is prompt (1–2 hours) after any method of administration When the drug is given continuously over a period of days, weeks, or months, excretion slowly rises to a maximum fluctuates irregularly about this level and continues for long periods after treatment is discontinued. There is thus evidence of storage in the tissues, which is most marked in the kidneys and the liver

An enormous amount of work has been done on the absorption and excretion of mercury particularly in this country by Cole Sollmann and their associates and abroad by Lomholt and others Most of it appeals to us as of more value in determining the possible dangers of toxic effects than in providing relative information as to therapeutic efficiency

The tissue changes produced by mercury.—In addition to the evidence provided by instances of mercurial poisoning in man, Kolmer and Lucke have conducted extensive studies of the pathological changes in animals treated with average therapeutic and with toxic doses of mercury The most striking lesions were of course in the kidneys where cloudy swelling, fatty degeneration frank necrosis and calcification especially in the convoluted tubules, always occurred. Insignificant changes were found in other organs.

After intramuscular injections of soluble or insoluble salts, similar lesions to those produced by injections of bismuth are found in the muscles (see Chapter VIII)

The toxic reactions produced by mercury.—The common toxic manifestations produced by mercury are

1 Stomatitis
2. Gastro-intestinal disturbances—colitis, etc.
3 Renal damage.

Very rarely cutaneous reactions may occur There are also certain phenomena directly associated with the route of administration of the drug e.g phlebitis from intravenous injections, abscesses and oil embolism from intramuscular injection, cutaneous irritation from inunction bronchitis or bronchopneumonia from inhalation etc.

Stomatitis.—Ulcerative stomatitis is the bane of mercurial therapy It is more frequent in patients with poor dental hygiene but can be made to appear in practically every patient by excessive dosage. Many individuals seem unusually susceptible, becoming salivated on amounts of drug which in others may be doubled or trebled without difficulty The lesion is due according to Almkvist, who has studied the subject exhaus-

fact that, during the years it was in general use the drug was always given by inunction rather than by injection.

Mercury is definitely contra indicated in the presence of pre-existing renal damage unless this is undoubtedly due to syphilis. Since the differential diagnosis of syphilitic nephritis, except the forms which sometimes occur in association with early syphilis, is difficult, and since the arsenicals, especially neoarsphenamine, are more suitable drugs to employ for a therapeutic test than either of the heavy metals, the question of employing mercury in the treatment of syphilitic nephritis rarely arises. In other forms of nephritis, it should rarely if ever be given, and then only under expert supervision.

Skin eruptions due to mercury.—When mercury is administered by inunction, and especially if the rubbing is too energetic or the areas rubbed very hairy a folliculitis may occur which is easily remedied by a change in technique or by abandonment of the method. In certain patients with "irritable" skins especially those with a pre-existing tendency to seborrheic dermatitis, inunctions may be impossible because of cutaneous irritation.

Other dermatoses, due to the use of mercury by various routes, and varying widely in appearance, from purpura and herpes zoster to exfoliative dermatitis, have been reported. They are, however so rare that no cases have been observed in our clinic. The subject has been reviewed by Almkvist and Wright.

Preparations of mercury and their routes of administration.—Considerations of relative toxicity and therapeutic efficiency have limited the use of this drug in our own clinic to seven preparations given by three different routes of administration. Since these seven preparations accomplish all that can be asked of mercury in a large syphilis clinic, it is unlikely that the practitioner will need to experiment with a larger number and it is therefore unnecessary to devote space to a detailed description of archaic, obsolete, and dangerous methods of administration. In Table 27A is provided a brief and summarized commentary of the various routes of administration which have at one time or another been in common use the preparations which we have found suitable under these different circumstances the dosage of each the advantages and disadvantages of each method and the indications for employing each of them.

With mercury by inhalation we have had no personal experience. There is nothing to be gained by this method, and we do not advise its use.

The administration of the drug by mouth is, from the therapeutic standpoint, the least efficacious of all methods. It is productive of some mild therapeutic effect, however and may be employed for the treatment of elderly patients especially for whom the intensity of treatment provided by the injection of any drug seems too great. A suitable situation sometimes arises in such an elderly individual who suffers with mild symptoms due to late syphilis which do not materially endanger health or life, and from whom it is desired to withhold the shock of the diagnosis of syphilis. To give any form of injection therapy might be revelatory mouth medica-

tion accomplishes all that is necessary without disclosing the nature of the disease. Two preparations one solid, the other liquid have been satisfactory in our hands These are the protiodide pill and so-called mixed treatment. This consists of a solution of the bichloride in an excess of potassium iodide, thus forming the biniodide, as follows

Mercury bichloride	0 1 gm
Potassium iodide	16 0 gms.
Water to make	120 0 cc.

Treatment by mouth has no place in the management of early syphilis

The intravenous or intramuscular injection of soluble salts is a satisfactory method of administering mercury when it is desired to obtain a prompt and rapid therapeutic effect. Such situations arise in some patients with late hepatic, cardiovascular or central nervous system syphilis in whom it is desired to avoid a Herxheimer reaction from the use of arsphenamine. To wait for the relatively slow therapeutic effects of insoluble bismuth salts or the even slower effect of mercury by inunction may seem undesirable Five soluble preparations are listed in Table 27A. The dosage of four of these succinimide, cyanide oxycyanide and benzoate is identical. The sulphide is given in larger doses but administered at less frequent intervals than the other four Practically we have confined ourselves almost entirely to the succinimide and the sulphide which are less likely to produce thrombosed veins or toxic effects than the others. The latter is the newest of the mercurial preparations and is considered by some (Stokes) the only safe one for intravenous use. It was introduced in the treatment of syphilis by Gennerich in 1931 and has been studied in this country by Wakerlin Lawless and by Freeman and his collaborators It is, according to Wakerlin, the most effective of all the mercurials in the treatment of rabbit syphilis both in the healing of lesions and the sterilization of lymph nodes In an experience covering more than 15 000 injections, given both intramuscularly and intravenously one of us (Kemp) has found it to be less nephrotoxic than bismuth and entirely free from local reactions when administered intramuscularly It has the disadvantage of having to be administered twice weekly and of causing, even with the most careful technique, a permanent bluish discoloration of the tissues at the site of injection

The various organic mercurials which have been proposed in this country especially mercurosal and flumerin possess no marked advantage over the simpler preparations, are more prone to produce serious reactions (we know of two deaths not from our own clinic due to mercurosal) and are gradually falling into disuse The chief objection to the use of soluble mercurial preparations by either route of administration is that being so rapidly absorbed and excreted, visits must be made to the physician daily or at least every other day causing undue loss of time and added expense for very little extra therapeutic gain. Further they are not suitable for prolonged treatment because of the high incidence of toxic complications. Thus their usefulness is practically limited to hospitalized or well-to-do ambulatory patients and in those at the start of treatment only When

TABLE 28

INSTRUCTIONS FOR THE PATIENT

THE RUBBING TREATMENT

READ THESE INSTRUCTIONS CAREFULLY

This is the best method of administering mercury but in order for the treatment to be successful, *it is absolutely necessary* (1) *For you to understand* each step of the method, and (2) for you to be willing to devote time and energy to it. SUCCESS OR FAILURE DEPENDS ON YOU

This ointment when rubbed on the surface of the body is absorbed by the skin. The medicine contained in it is taken up by the blood and carried to all parts of the body

DIRECTIONS FOR RUBBING

The best time to rub is before going to bed. *Take a hot bath beforehand*, or if a complete bath is impossible, wash well with soap and hot water the part to be rubbed that night.

When thoroughly dry take out of the jar on the end of a spoon or spatula, a *portion of ointment about the size of the end joint of your little finger* (as big as a large lima bean)[1] Spread a little of this portion on the skin and with the *flat palm of the hand* rub it in slowly and not too hard, putting on a little more ointment from time to time until the portion for that night has all been rubbed in. This ought to take *20 minutes* and you should *time yourself* by a clock.

Rub a different part of the skin every night of the week so that no part is rubbed more than once a week. The rubbing should be done over a *part of your skin four times as large as your hand.*

The best places to rub are—

First night.—Upper part of one thigh in front.
Second night.—Upper part of one thigh in back.
Third night.—Inner sides of both arms.
Fourth night.—One side between hip and armpit.
Fifth night.—Other side between hip and armpit.
Sixth night.—Upper part of other thigh in front.
Seventh night.—Upper part of other thigh in back
Eighth night.—Start all over again.

Your back is a good place to rub if you have someone to do it for you. *Avoid rubbing very hairy areas* such as the armpits. If *pimples break out* in any of these places you are rubbing too hard.

If after 20 minutes rubbing, any ointment seems to be unabsorbed, the excess may be wiped off the skin with a soft clean dry cloth, or if preferred, with a cloth soaked in a little benzine.

While taking this treatment *please report in person or by letter* (1) two weeks after starting the treatment, (2) once a month thereafter

Stop the treatment and report at once if

Your *teeth ache*.

Your *gums become swollen*, painful, inflamed or bleed easily

You have any *persistent pain, diarrhea, or headache*.

[1] At least one manufacturer (Parke Davis) puts up a weighed 4-gram dose of Unguentum Hydrarg in waxed paper (dispensed as "Mercurettes") This is the easiest method of prescribing the drug.

these various limitations are met however the method is unquestionably of value in providing rapid saturation with a heavy metal, especially since a satisfactory soluble bismuth preparation is not as yet available.

The intramuscular injection of insoluble salts (calomel, grey oil, and the salicylate are those which have been commonly employed) is inadvisable in modern syphilotherapy The injections are painful, produce ultimate fibrosis of the buttock, absorption occurs at an irregular rate, cumulative severe toxic manifestations are frequent, and if they occur are impossible to control since the injected mercury cannot be removed. The method has been completely replaced by the much safer and therapeutically more active method of intramuscular injection of insoluble bismuth salts.

The administration of mercury by inunction is the best method of use of the drug If the 50 per cent U S P ointment seems too irritating to the skin or if it produces rapid salivation, it may be diluted to 25–33 per cent with cold cream We have had no experience with the massive weekly inunction (Cole), which must be given by a trained attendant. Calomel ointment has been abandoned as inefficient.

Metallic mercury by inunction is therapeutically efficient though its initial action is slow requiring 4–6 weeks of daily rubs to produce an effect obtainable in a few days with arsphenamine. The method is safe and free from cumulative toxic effects. If symptoms of intolerance appear cessation of the drug and a hot bath afford prompt relief It is, moreover a distinct economic gain to the patient, who is freed from the necessity of frequent visits to the clinic or office. From this standpoint it might profitably be utilized even to replace bismuth in patients who cannot afford the financial drain of continuous treatment by injection. The chief drawback to the method is, of course, that, requiring to be carried out by the patient it is valueless unless his intelligent cooperation can be obtained. His objections that inunctions are dirty and time-consuming must be overruled by the argument of superior therapeutic effect and financial saving as compared with other methods of giving mercury It is our custom to provide the patient with typed or printed detailed instructions which are reproduced in Table 28

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Chapter X

THE IODIDES

The use of iodides in the treatment of syphilis rests purely on clinical and empirical grounds. From the clinical standpoint it has been known for nearly a hundred years that these drugs given alone have little or no effect on the lesions of early syphilis, but that in late syphilis, destructive cutaneous and osseous lesions (gummas) may be healed and the pain caused by them may be relieved with great rapidity. The action of the drug is apparently limited to its local healing effect, however, since in patients treated with iodides alone, recurrences of lesions at the same or a different site were not uncommon. In the pre-arsphenamine era it was customary to combine mercury and the iodides, the former for ultimate curative effect, the latter to promote rapid resolution of late lesions.

With the development of modern syphilology came the information that the iodides had no apparent effect on treponemes present in the lesions of early syphilis either in experimental animals (Nichols) or in humans, that their effect on reversal of the serologic tests in any stage of syphilis was minimal, if indeed any actually exists, and that the arsphenamines would heal most lesions, early or late, even more promptly than the iodides. Nevertheless these drugs continue in general use for two reasons: first, because certain symptoms or lesions, especially in osseous, visceral or neurosyphilis, seem clinically to be more rapidly alleviated when the iodides are given in conjunction with an arsenical or a heavy metal than when these latter are used alone; second, because empirically their healing effect may enhance the penetrability into relatively avascular lesions of the more powerful treponemicidal drugs. Indeed, for this latter reason iodides are usually employed at some time in all patients with syphilis, early or late, whether or not obvious lesions are present, on the assumption that hidden lesions may exist into which the penetration of arsenic and the heavy metals may be augmented.

The exact evaluation of the worth of the iodides in modern syphilotherapy, combined as they must be with other more powerful antisyphilitic drugs, is to our way of thinking impossible. It may well be that aside from their effect in accelerating the healing of outspoken late lesions they have no influence of any kind on the ultimate outcome, measured in terms of "cure" or arrest. Indeed, in early syphilis, we are inclined to think that this is probably the case and that patients treated with an arsenical and a heavy metal alone do quite as well as those to whom iodides are also given. However, their undoubted healing power in late syphilis and the theoretical consideration that they aid in the destruction of treponemes by enhancing the penetrating powers of other drugs are considerations too alluring to pass by, and we share the general feeling that they still have a place, even if an humble one, in the management of most patients with syphilis.

The mechanism of action of the iodides —The non-specific nature of the action of the iodides is apparent, not only from the demonstration of their failure to kill treponemes, but also from the fact that they exercise a marked resolving effect in the lesions of other granulomatous diseases than syphilis, such as tuberculosis, leprosy and the various fungus infections, especially actinomycosis, sporotrichosis, and blastomycosis. The mechanism by which this is accomplished is not definitely known. The most logical suggestion seems to be that of Jobling and Petersen. There is present in normal blood serum a substance (antiferment or antienzyme) which inhibits the proteolytic effects of trypsin. These workers found that following the administration of iodides, the antitryptic activity of the blood serum of guinea pigs and human beings was markedly reduced. In granulomatous and necrotic tissue, proteolytic ferments exist, the action of which is, under ordinary circumstances, impeded by the antiferments of the blood. According to the interpretation of Jobling and Petersen, iodine neutralizes the antiferment of the blood and permits the action of the proteolytic ferment in the lesion with the subsequent solution and absorption of necrotic tissue.

The pharmacology of the iodides —The following statements are based largely on Osborne s work. When given by any route, iodides are rapidly absorbed and excreted. Iodine appears in the urine within a few moments after administration, reaches a peak at the second to fourth hour and is practically entirely excreted, no matter what the size of the dose, within 96 hours (60–80 per cent within 24 hours) Almost all of the drug is excreted in the urine. The absorption of sodium and potassium iodide is approximately equally rapid. Given by mouth, 96 per cent of the drug administered is promptly absorbed by rectum only 20–25 per cent is absorbed. For intravenous use, sodium iodide is preferable to potassium iodide because of the toxicity of the potassium ion. Iodine is stored in the tissues only in very small quantities if at all. It appears in the cerebrospinal fluid only in traces when the drugs are administered by mouth, but when sodium iodide is given intravenously appreciable quantities may be found in the spinal fluid

Loeb and Fujisawa have each demonstrated that the concentration of iodine in syphilitic tissue is greater than in uninvolved portions of the body This may have some bearing on the effect of the drug in syphilis.

The choice of iodide preparations —Since potassium iodide and sodium iodide are so readily absorbed, since the symptoms of intolerance they produce are so relatively infrequent and insignificant, and since they are cheaper than the various elaborate organic compounds which have been advocated by proprietary manufacturers there seems to be no reason for adopting more complex substances. These two are satisfactory for all except the rarely intolerant patient. We have never found occasion to employ any other iodide preparation. Sodium iodide is said by Osborne to be more easily tolerated by most patients than potassium iodide in addition, it is absorbed slightly more rapidly It is, however slightly more expensive.

Very rarely a patient will be encountered who is so sensitive to the

inorganic sodium and potassium iodides that he *cannot take them with comfort.* If the administration of iodide seems essential in such a patient, it may sometimes be accomplished by the use of such preparations as sajodin (1–3 grams daily)

Methods of administration —Since the iodides are so readily absorbed, either in large or small dosage, when given by mouth there is little indication for their administration by any other route. Either sodium or potassium iodide may be employed, more usually the latter The drug is prescribed in concentrated solution i.e.

Potassium iodide	100 0 grams
Water	100 0 cc.

in which 1 drop equals approximately 0 065 gram (1 grain) or in such concentration that one teaspoonful (4 cc.) contains the desired dose. We have seen no advantage in the use of more elaborate elixirs, syrups, etc. as solvents The solution turns yellowish brown on standing, but is not thereby spoiled. The desired dose must be administered *well diluted* in a full glass or more of drinking water or in milk to disguise the taste, and is a little less productive of gastric irritation if given one half hour *before* meals.

Rectal administration is undesirable, since only 20–25 per cent of the drug is absorbed, and in dosage exceeding 30 grams daily there is usually severe rectal irritation.

The daily intravenous administration of sodium iodide in sterile 10 per cent solution (sterilised by boiling) has been advocated by Stokes for the treatment *of certain forms of neurosyphilis especially acute syphilitic* meningitis. The recommendation is made largely on the basis of Osborne's work showing the increased iodine content of the cerebrospinal fluid after this method of treatment. The dose usually starts with 5 grams (50 cc.) increasing rapidly to a daily dose of 10 grams (100 cc.) and prolonged for a series of 10–30 injections. The method should not be attempted unless the patient's potential sensitivity to iodides has been tried out by a few days' preliminary administration by mouth. The drug may be given simultaneously by mouth and intravenously We have tried the method in a number of cases, and have not been impressed with its claimed superior efficacy It is expensive tends to thrombose veins is useful only in hospitalized patients (because of the inconvenience and expense of daily visits to the physician's office) and accomplishes little more so far as we can see than the use of large doses of iodide by mouth. For general application by the practitioner the method is not advised.

The dosage of the iodides —An old custom grown up over a period of many years, is to start the administration of potassium iodide by mouth in small doses (0.3–1 0 gram three times a day) and to increase by small increments *(0 065 gram) at each dose or each day until the desired dose* is reached. We see no point in this. There is no objection to administering an initial dose of 2–3 grams three times daily Symptoms of intolerance are no more frequent than with smaller doses.

There is some debate as to the maximum average desirable dose some

physicians favoring small (1–3 grams daily), others very large doses (10–30 grams daily) For the average patient with syphilis, early or late, we favor a daily dose, divided into three portions of 6–12 grams. In only one circumstance, acute syphilitic meningitis, do larger doses than this seem to accomplish more prompt results. In this condition, a daily dose of 10–50 grams by mouth may be given, sometimes with spectacular symptomatic improvement.

Special indications and contra indications for the iodides —The particular indications for the immediate use of iodides, at the start of treatment in combination either with an arsphenamine or a heavy metal are late gummatous lesions in any location, for the prompt relief of pain in bone lesions, in hepatic syphilis of all types, in cardiovascular syphilis, and in acute syphilitic meningitis. In all other types of syphilis, it is customary to combine the use of iodides with the heavy metals, but not with arsphenamine, at some time during the course of treatment. Less than 3–6 months total use of the drug is probably of no value

Excepting the rare instances of intolerance, the only contra indications to the use of the iodides are in tuberculosis, especially with pulmonary involvement, and in goitre, whether simple or toxic. In tuberculosis, the resolving effect of the drug on granulomatous lesions may result in a disastrous spread of tuberculous infection. In some instances of simple goitre toxic hyperthyroidism may be produced, or in toxic goitre made worse by the administration of iodides.

Intolerance to the iodides —The patient about to take iodides should be warned that almost immediately after starting the drug he may develop coryza—a watery nasal discharge—that he may have an unpleasant aching sensation at the angles of the jaw (iodide mumps) and that he will have a brassy taste in the mouth, due to the excretion of small quantities of drug in the saliva. Unless these symptoms are very annoying they may be disregarded. Sometimes oddly enough, they may be completely obviated by doubling the dose. The explanation for this is not clear Sometimes mild symptoms of gastric irritation—nausea, anorexia, and diarrhea—appear

Most patients will also develop after 2–3 weeks use of the iodides, a mild skin eruption—iodide acne—on the chest and face (in the seborrheic areas) This also may be disregarded unless so extensive as to upset the patient for cosmetic reasons.

Very rarely—so rarely that we have never seen a case—a patient is completely intolerant to the drug. A single initial dose is followed by the utmost congestion of the nasal mucosa, by edema of the tongue lips and glottis even perhaps so severe as to necessitate tracheotomy or by generalized edema. To such patients the drug cannot be given

Almost equally rarely the prolonged administration of iodides may result in very severe and sometimes fatal generalized skin eruptions analogous to those produced by bromides. These lesions are often bizarre described as verrucose, vegetating tuberose nodose fungating and bullous. We have seen only one or two such patients among some forty thousand or more to whom iodides have been given though a perusal of

the dermatologic literature would impress one with the apparent frequency of severe iododerma. For the practitioner it is enough to remember that bizarre skin eruptions appearing during the administration of iodides may be due to these drugs and that such eruptions usually involute rapidly as soon as iodides are discontinued. Wile suggests that healing may be speeded and symptoms of general toxicity lessened by the intravenous administration of sodium chloride, on the basis of substitution of chloride for iodide ion in the blood and the accelerated excretion of iodine.

In a few instances, particularly in patients with hepatic syphilis, we have seen fever produced by the use of iodides (*Katzenstein*) The temperature, normal before the drug is started, may become irregularly elevated within a few days to levels commonly between 37.2°C (99°F) and 38.3°C (101 F) but exceptionally to 40°C. (104 F) promptly to subside as soon as iodides are discontinued. This has been ascribed by some observers to absorption of necrotic tissue (as from an hepatic gumma) but this can hardly be the correct explanation, since Barker and Wood have recently reported severe febrile reactions to potassium iodide in non-syphilitic patients with advanced hyperthyroidism. The cause of the reaction is not clear If it occurs on repeated trial of the iodides this form of therapy should be abandoned.

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Chapter XI

THE TECHNICAL ASPECTS OF TREATMENT PREPARATION OF THE ARSENICAL DRUGS TECHNIQUE OF INTRAVENOUS AND INTRAMUSCULAR INJECTION LUMBAR PUNCTURE CISTERNA PUNCTURE

In the preparation of drugs for intravenous or intramuscular injection, the practitioner will do well to read carefully the manufacturer's instructions which accompany each ampule. In this chapter the essentials are briefly presented with omission of credit for the work on which various points are based. It is possible, though unnecessary to make an extremely complex procedure of the administration of the arsphenamines. We present the steps of preparation in the simplest possible form. The following paragraphs are in part quoted and in part modified from "The Management of Syphilis in General Practice," which was prepared in 1929 and revised in 1938 for the United States Public Health Service. The technical portions of this publication were in turn based on a previous official statement for use by the medical departments of the Army the Navy the Veterans' Bureau, and the Public Health Service by G C Lake in 1922. Such modifications as we have introduced are those which seemed to us possible or desirable in office as contrasted with clinic practice

Inspection of the ampule —It is obligatory to read the label carefully before use. Fatal accidents have occurred even in experienced hands, by the administration of acid arsphenamine in place of neoarsphenamine through neglect of this precaution. The name of the drug and the dosage must be recorded the name of the manufacturer and the lot number may be useful in the event of serious reaction.

Cracked ampules should be discarded, as should also those in which the powdered drug (of any of the preparations) is lumpy and not freely mobile or in which a color change has taken place (arsphenamine should be pale yellow to lemon yellow neoarsphenamine lemon yellow to canary yellow silver arsphenamine dark brown mapharsen white or light gray) Ampules of suspicious color should be forwarded to the National Institute of Health, Washington D C for examination

The solvent —Sterile freshly distilled water is used in the preparation of all the arsenical drugs. Single distillation is adequate sterilization is accomplished by boiling for 5 minutes An aqueous solution of any of these products is suitable for intravenous administration. An added refinement of technique desirable but not essential with arsphenamine (606) though not with other products, is the use of sterile freshly prepared normal salt solution (0.85 per cent) to bring the aqueous solution up to desired volume. This procedure reduces the risk of thrombophlebitis.

The Preparation and Administration of Arsphenamine

1 Inspect the ampule read the label.

2 Place in a sterile Erlenmeyer or Florence flask (capacity 50–1000 cc., depending on the size of the dose to be prepared) a small but unmeasured quantity of sterile freshly distilled water roughly 5–10 cc. per decigram of drug (i.e., 20–40 cc. for 0.3–0 4 gm. 200–400 cc. for 3 0–4 0 gms.)

3 The water may be cool or hot (70°C –160°F) With the products of some manufacturers (see directions with the ampule) hot water facilitates solution and does not increase toxicity

4. File the neck of the ampule break it off, and sprinkle or dust (do not dump) the powder on the surface of the water Arsphenamine is slowly soluble and tends to agglutinate into gelatinous clumps If allowed to stand, 10–15 minutes are necessary for solution this may be hastened by sealing the flask with a sterile rubber stopper followed by vigorous shaking. There is no danger of increased toxicity from shaking (aeration) of acid solutions of arsphenamine

5 *Do not administer the acid solution it must be alkalinized or death may result*

6 After complete solution is obtained the drug is ready for alkalinization. Do not use any solutions in which flaky or gelatinous particles are still floating.

7 Alkalinization may be accomplished by the exact or the approximate methods. The United States Public Health Service and all manufacturers advise the former It is customary and advisable to use either normal (4 per cent) or 15 per cent sodium hydroxide solution * though for the approximate method a solution of unknown concentration may be employed.

Exact method —With a sterile pipette or burette add all at once to the clear solution of acid arsphenamine 0.85 cc. of 4 per cent or 0.227 cc of 15 per cent sodium hydroxide solution per decigram of drug, i.e. for 0 4 gm arsphenamine use 3 4 cc. of 4 per cent or 0 9 cc 15 per cent alkali. These figures represent the correct amount of sodium hydroxide to form the disodium salt of arsphenamine They include an excess of one-third of that amount necessary just to redissolve the precipitate which first forms.

Some workers including ourselves, feel that the danger of thrombophlebitis is greater and the risk of other reactions only slightly less, when the disodium salt is used (because of excessive alkalinity) than with a mixture of the mono- and disodium salts. Such a solution and we recom-

* Enough sodium hydroxide solution can be prepared at one time to last for a month or longer provided it is kept in a rubber-stoppered, wax-lined or paraffin-lined bottle. There is danger of deterioration on account of absorption of CO_2 from the air and of reactions with the glass container A wax-lined bottle may be prepared by placing wax or paraffin in a bottle, sterilizing with dry heat, and spreading the melted wax by rotation over the inside of the bottle as it is cooling. If precipitate is found in the alkali, it is probably an evidence of deterioration of the solution, which should be discarded For use in large clinics, a 2-liter bottle protected from the action of the alkali and of the atmospheric CO_2 and set up with an automatic measuring burette is a great convenience and will insure the safe-keeping of the alkali for a long period.

mend its use, may be prepared by adding only one-fourth excess of alkali (i.e., 0.64 cc. of 4 per cent or 0.212 cc. 15 per cent alkali per decigram of drug)

The approximate (drop) method.—While the exact method is used in most larger clinics, the approximate method suffices in office practice, including our own. Whether or not the concentration of the alkali solution is known, it is added drop by drop until the yellow precipitate which first forms completely redissolves. The drops should be counted. Resolution of the precipitate should be facilitated by a swinging rotary motion of the flask, but not by shaking, since now aeration (oxidation) increases toxicity. When the precipitate is completely redissolved, add one-fourth excess of alkali (i.e. if 12 drops were necessary to redissolve add 3 extra drops) *

8. The final dilution of the solution should be from 10–30 cc per decigram of drug (i.e. 40–120 cc. for a 0.4 gm. dose). The United States Public Health Service advises the larger amount. In our own clinic we employ a dilution of 20 cc. per 0.1 gm. drug. The incidence of mild reactions is certainly less with the more dilute solutions. The final dilution may be with sterile water or if desired, with sterile normal salt solution. The latter reduces the risk of thrombophlebitis.

9. Filtration of the solution through sterile filter paper cotton or gauze, is usually advised. This procedure is always employed in our clinic but in office practice we find it unnecessary.

10. The properly alkalinized and diluted solution should stand for about 30 minutes before administration to permit completion of the chemical reactions. Toxicity is actually reduced by this delay. The solution may be allowed to stand for as long as three hours without increase in toxicity provided it is protected from the air is not shaken, and the room temperature does not exceed 30°C.

11. A gravity apparatus (graduated cylinder rubber tubing† 4–6 feet long containing a glass window a few inches above the lower end, Mohr pinchcock for cutting off the flow Luer adapter stainless steel needles with slip joint 19–20 gauge) properly sterilized before use, is preferable for administration. In its absence a 50 cc. syringe may be used, though this is less desirable since (1) the rate of flow is harder to control (2) the solution of the average dose is too concentrated and (3) such large syringes are expensive and the breakage rate is high.

* The pH of a proper solution is about 10, and it is impossible to buffer it to neutrality with common buffers without precipitation. Moreover the alkaline solution is well tolerated if given slowly and well diluted. Underalkalinization may be productive of serious generalized reactions. Overalkalinization causes pain along the vein during injection and subsequent thrombosis sometimes it may cause actual constriction of the vein wall, rendering the immediate completion of the injection impossible.

† Caution.—Before being used the first time the tubing should be filled with 4 per cent sodium hydroxide solution for not less than six hours. It should then be thoroughly rinsed in water sterilized by boiling, and then thoroughly rinsed with sterile water again just before using. This is in order to prevent the tubing reaction (see Chapter VII).

12. The gravity apparatus should be arranged to provide a column of fluid not over 3 feet in height. The tubing is rinsed with sterile water the cylinder and tubing are filled with solution and the air* expelled by lowering the end of the tube below the level of fluid in the cylinder

13 The patient should lie comfortably on his back on a couch or treatment table.

14 Insert the needle and proceed with the injection (see below)

15. *The rate of injection.*—If the specifications as to the gauge of needle, etc. have been followed, the correct rate of injection is practically insured, i.e., by the size of the needle and the length of the tube however, this should not be taken for granted, but the exact time should be observed, and in no case should the rate exceed 25 cc. in one minute or a dose of 0 4 gram in four minutes five minutes is preferable. The rate of flow should be even as well as slow Should the patient show any signs of an immediate reaction, stop It is highly desirable, in sensitive patients, to wait a minute or two after injection of the first 0 1 gram before proceeding with the rest of the injection When the necessary amount has been injected cut off the flow with the pinchcock, disconnect the tubing, allow a few drops of blood to escape then withdraw the needle and place sterile gauze over the puncture, instructing the patient to hold the gauze there for a few minutes If another injection is to be given and there is any suspicion of contamination of the tubing with blood empty the cylinder and start over with a new sterile tube.

The Preparation and Administration of Neoarsphenamine

The administration of neoarsphenamine is much simpler than that of arsphenamine Neoarsphenamine is readily soluble in a small quantity of water and need not be alkalinized. It may be given by the syringe method. There is no advantage to the gravity method with this drug

1 Inspect the ampule read the label.

2 Prepare only a single dose at one time, or in any case, no more than can be administered within 20 minutes.

3 Place in a small sterile beaker or medicine glass 10–15 cc of *cool* sterile freshly distilled water (Hot water cannot be used it increases oxidation and toxicity)

4. Open the ampule and sprinkle the contents on the surface of the water The drug is readily soluble and will go into solution promptly with no agitation whatever Shaking the solution or squirting it back and forth from a syringe increases toxicity and should be avoided.

5 The solution should be perfectly clear and transparent cloudy or flaky solutions must be discarded

6. The concentration of the solution is less important than with arsphenamine. The United States Public Health Service advises a dilution of 10 cc. per 0 1 gm. drug but much more concentrated solutions are

* The danger of air embolism is commonly exaggerated and the intravenous injection of 4–6 cc. of air does no harm. It should of course be avoided but physician and patient need not be unduly alarmed if it occurs.

usually employed. In office practice we use roughly 15–20 cc. water for the average therapeutic dose (0.3–0 9 gm.)

7 *Do not add alkali*

8. Filtration is unnecessary

9 The solution should be injected immediately and in no case longer than 20 minutes after preparation. Standing increases toxicity

10 The only apparatus necessary is a sterile all glass Luer syringe 20–30 cc. capacity, with stainless steel needles, 20–24 gauge.

11 The injection must be given slowly to avoid immediate reactions. Three to six minutes are none too long for a 0 6–0 9 gm. dose.

The Preparation and Administration of Silver Arsphenamine

This drug must be injected intravenously either syringe or gravity methods may be used. We employ the former

1. Inspect the ampule read the label.

2. Prepare only a single dose at one time or in any case, no more than can be administered within 20 minutes. Never use left-over portions.

3 Place about 15 cc. of *cool* sterile freshly distilled water in a small sterile beaker or medicine glass. (Hot water may not be used)

4 Open the ampule, rotate it gently to loosen its contents, sprinkle the powder on the surface of the water and allow it to dissolve without agitation. Solution will be complete in about 5 minutes. Do not shake, stir or squirt aeration increases toxicity

5. The solution should be perfectly clear like black coffee Cloudy solutions or those containing insoluble matter should be discarded.

6. The concentration of the solution should be slightly less than with neoarsphenamine, e.g. 25–30 cc. of water for 0.3 gm drug.

7 *Do not add alkali*

8. Filtration is advised by the manufacturers, but in our experience is unnecessary

9 The solution should be injected immediately and in no case longer than 20 minutes after preparation. Standing increases toxicity

10 Inject slowly and evenly Allow at least 3–4 minutes for injection.

The Preparation and Administration of Sulpharsphenamine

This drug must be given intramuscularly it should never be used intravenously

1. Inspect the ampule read the label.

2. Select an ampule containing the proper dosage and with a sterile 2 cc. Luer or tuberculin syringe (preferably the latter) add to the ampule 1–2 cc. of *cool* sterile water (1 cc for doses 0.3 gm. or less, 1 5 cc. for 0 4–0 5 gm. 2 cc. for 0.6–0.8 gm.) Highly concentrated solutions are better tolerated than dilute solutions. The drug is rapidly soluble.

3. Aspirate the solution into the syringe and inject intramuscularly (see below)

The Preparation and Administration of Mapharsen

This drug is to be given intravenously by syringe

1 Inspect the ampule read the label.

2 Select an ampule containing the proper dosage. Several doses may be prepared at the same time as standing and aeration do not increase toxicity Place in a sterile container *cool* sterile freshly distilled water to the amount of 5–10 cc. for each dose. Add the drug to the water It dissolves readily *Squirt the solution back and forth several times with a syringe to promote aeration* (observe that this is the direct opposite of all the arsphenamines)

3 Aspirate the desired amount of solution and inject *rapidly*

The Preparation and Administration of Bismarsen

This is identical with that of sulpharsphenamine. The manufacturers supply a solvent containing 0.25 per cent butyn (to minimize pain) but in our experience sterile distilled water is equally satisfactory The drug may be mixed in the ampule or in a sterile medicine glass 1 5–2 cc. of water is adequate to dissolve the 0 2 gm dose. *Administration is intramuscular*

The Preparation and Administration of Tryparsamide

This drug is an easily soluble white powder The maximum dose of 3 0 grams may be dissolved in 10–20 cc. of sterile freshly distilled water and administered by the syringe method. Unlike the arsphenamines, toxicity is not increased by heat or aeration (shaking and squirting to effect solution is permissible) and the speed of injection is unimportant. Immediate shocklike reactions do not usually occur

In rare instances when the patient has no veins suitable for intravenous injection tryparsamide may be given intramuscularly in concentrated solution (3 0 gms. in 3 cc. of water)

General Considerations on the Intravenous Administration of the Arsenicals

Intravenous treatment is actually a simple procedure. While all glassware used in preparation of the drugs, all solutions and all instruments (gravity apparatus, syringes, needles) must be sterile, it is unnecessary for the operator to be clothed, as for a surgical operation, in sterile gown, rubber gloves etc.

Elaborate precautions on the part of the patient are likewise unnecessary If there is a tendency to constipation a mild cathartic should be taken the night before treatment this reduces the incidence of gastrointestinal reactions It is wise, for the same reason, for the patient to avoid food for the 2–3 hours immediately preceding and for a few hours following the injection. Treatment may safely be administered to ambulatory patients, who may be allowed unless an immediate reaction has developed to leave the office as soon as the injection is completed. It is wise to plan the hour of treatment for the late afternoon, so that if the patient is incommoded at all he may go home rather than back to work.

The discomforts of treatment should be minimized as much as possible

by the expertness of the operator and by the use of sharp uncorroded, stainless steel needles.

The Technique of Intravenous Treatment

We purposely omit illustrations and several pages of description of the method of giving intravenous treatment. After a considerable experience in this field, we feel that a satisfactory technique can be secured only by actual practice not by reading about it or by studying pictures. The in experienced physician will learn much more by volunteer service in a nearby large syphilis clinic, first as observer for a day then as operator in fifty or so cases under the supervision of an expert, than he can by study of the printed page. Any physician who does not know how to give an intravenous injection has no right to treat syphilis until he has acquired the knowledge by actual experience under supervision. We mention therefore, only a few important points.

Needles should be stainless steel to prevent external corrosion. They should be of medium bevel with pointed rather than rounded tips. They should be cleaned after each using, and a stylet inserted. From time to time they should be tested for internal corrosion by bending the point on the hub The gauge depends on the drug —for arsphenamine 18–20 gauge for other drugs 21–24 gauge, depending on the size of the vein selected. Above all the points must be sharp and must be kept so by retouching after every 10–20 punctures. Sharpening had better be done by an instrument dealer than by the physician. A dull needle makes a dissatisfied patient.

The intravenous injection may be given either in the sitting or recumbent position, the latter always with arsphenamine by the gravity method and with any drug in a nervous patient.

The most appropriate veins are the median cephalic or median basilic, at the bend of the elbow (cubital space) Other veins even including the small ones in the wrist or on the back of the hand may be used if necessary The overlying skin is cleansed with an alcohol sponge sterilization with iodine is not necessary nor is local anesthesia. A bandage, or a rubber tube and hemostat, is a satisfactory tourniquet. The veins may be made to stand out more visibly if the patient clenches his fist tightly or if the operator smartly slaps the surface of the arm over the vein.

The vein is fixed by downward traction of the skin with the thumb of the left hand. The needle is inserted at an obtuse angle through the skin just above or slightly to one side of the vein is then advanced about 0.5 cm. and the vein wall punctured. *A free flow of blood must be obtained before the injection is given.* If a gravity apparatus is used this may be deter mined either by inserting alone the unattached needle or with the entire apparatus connected by means of a three-way stopcock attached just behind the needle. With the syringe method, a retrograde column of blood must enter the barrel before any drug is injected. (Since blood is visible with difficulty in a solution of silver arsphenamine, it is often wise to insert the needle attached to an empty syringe the transfer to the full one being made after the vein is entered.)

Injection should never be started until the operator is sure the needle is in the vein It should be terminated at once if it produces a visible subcutaneous lump or if the patient complains of sharp burning pain at the site of injection. Leakage of solution into the tissues is to be rigorously avoided it may be due to (1) a clean miss of the vein (2) failure to introduce a long beveled needle far enough into the lumen (3) pushing the needle too far through the posterior vein wall

Blood for serologic testing may be obtained (a) before the injection is given, through a needle unattached, or attached to a clean empty syringe or through the three-way stopcock of the gravity apparatus, or (b) after injection, by detaching the syringe or gravity apparatus from the needle which is still in the vein reapplication of the tourniquet, discarding of the first dozen or so drops of blood,* and allowing the flow of 3–5 cc. of blood into a small test-tube

We emphasize again that with the exception of mapharsen, all drugs should be administered slowly both by gravity and by syringe. Mapharsen should be injected speedily

After the needle is withdrawn, the patient makes pressure over the puncture wound for several minutes with a sterile gauze sponge or cotton pledget. A bandage is not necessary

The Technique of Intramuscular Injection

"The buttocks are the most suitable muscle masses to utilize in the treatment of syphilis. *Intramuscular injections should be given into the upper outer quadrant of the buttock* If given in the upper inner quadrant, one is likely to strike bone or to deposit the injected material near the roots of the sacral plexus, from which a troublesome sciatica may result. If given in either lower quadrant, there is pain on sitting and there is more danger of striking the sciatic nerve or large vessels.

"The only apparatus necessary is a 2 cc. Luer all-glass syringe and 18 to 20 gauge needles 1 5 to 2 5 inches long, depending on the fatness of the buttock to be injected. These instruments should be sterilized by boiling, *not* by alcohol. *The syringe is filled with the substance to be injected before* the needle is attached. If the drug to be injected is in suspension in a thick oil or fat, the syringe should be filled while hot so that the mass may be liquefied

"The patient lies face down on a long table thoroughly relaxed, and with his feet toed in. After preliminary sterilization of the skin with iodine and alcohol, *the operator draws the buttock down with the left* hand toward the patient's heel to fix the tissues The needle may be inserted separately or attached to the syringe. A separate insertion is preferable, since if a large vessel is accidentally struck, blood will flow from the needle. In either case however a deep insertion is made with a short, sharp stroke the direction of the needle being slightly inward and downward from the vertical.

Even though no blood appears at the needle hub aspiration should always

* The first few drops of blood wash out the drug remaining in the needle. Unless this is done, the serologic test may be unsatisfactory

be done as soon as the syringe is attached and before any material is injected. The injection of an insoluble salt (especially bismuth) in oil suspension into a vein is always accompanied by distressing symptoms of pulmonary oil embolism and may result fatally If blood does flow from the needle or is obtained even in the smallest amount on the subsequent aspiration the needle must be withdrawn and reinserted at least 1 cm. or more from the original puncture.

As soon as it is apparent that no blood can be aspirated the injection may be made. The suspension or solution should be followed by the injection of 1 cc. of air to clean the needle and prevent leakage along the needle track. The needle is then rapidly withdrawn, and the site of the injection massaged vigorously for two or three minutes. Alternate buttocks should be used for injection.

"Painful superficial nodules or lumps are usually due to too shallow injection or leakage along the needle track and are best treated by local heat and massage. Large deep indurations may result from a too deep injection With proper care for sterility abscesses should not occur except with sulpharsphenamine. With this drug, especially in infants a sterile abscess may occur about once in a thousand injections.

Lumbar Puncture

Expertness in the technique of lumbar puncture likewise cannot be attained by reading about it, nor by studying pictures or diagrams. It is essential to see the procedure actually carried out, and to perform it repeatedly oneself Well done, it is a simple and almost completely painless operation, actually entailing less discomfort than venepuncture poorly done, it may mean physical agony for the patient and mental anguish for the physician. If the practitioner undertaking the management of syphilis is not already adèpt in the technique he should refer his patients to an expert to have the test made or else, before attempting it alone, he should familiarize himself with the landmarks, watch its repeated performance by someone else, and finally perform a series of punctures under close supervision. A painful spinal puncture destroys the confidence and cooperation of many patients.

Explanation to the patient for the necessity of lumbar puncture —It is rarely difficult to obtain the patient's consent for lumbar puncture, provided the physician's attitude toward it is as matter-of-fact as toward urine or serologic testing In most instances it is unnecessary to ask consent the patient is told simply that the test is necessary It is usually desirable to explain the rationale i e. that the nervous system is involved in about 25 per cent of all patients with syphilis, that this involvement is manifest in the cerebrospinal fluid years before it has caused clinical damage that if the fluid is abnormal steps may be taken to prevent the development of the dreaded nervous sequelae and that if it is negative fairly definite assurance of future safety in this domain may be given. Only the most stupid careless, or uncooperative patients will refuse the test after such an explanation.

The dangers of and contra indications to lumbar puncture —

In all but the exceptional patient with syphilis lumbar puncture is a perfectly harmless procedure There is not the slightest risk of damage to the spinal cord by the needle. Patients who refuse the procedure because a friend was paralyzed after it was done fail to understand that the paralysis was due to the disease for which lumbar puncture was performed, and not to the operation itself

The two absolute contra-indications to lumbar puncture are brain tumor especially if subtentorial and acute infections. In the former case, the sudden release of intracranial pressure may prove rapidly fatal through herniation of the brain stem into the foramen magnum with paralysis of respiration. Puncture should never be performed in patients with symptoms or signs (particularly choked discs) of increased intracranial pressure, except under the supervision of a neurosurgeon, who must be prepared to interfere surgically in case of necessity In the case of acute intercurrent infections the alterations in the blood-spinal fluid barrier caused by the withdrawal of spinal fluid may permit the transfer of organisms from blood stream to the cerebrospinal canal with the subsequent production of meningitis

A relative contra indication is recent subarachnoid or extradural hemorrhage, especially that type associated with marked hypertension. Other forms of cerebral hemorrhage are less to be feared. If performed too soon after subarachnoid hemorrhage, release of spinal fluid may permit further bleeding It is wise to delay puncture for at least two weeks after the vascular accident. Other relative contra-indications are advanced age (but not infancy or childhood) pregnancy or illness from causes outside the nervous system so serious as to make the information provided unimportant.

Deaths have infrequently occurred as a result of lumbar puncture (Wieder) The vast majority of them have been in patients with brain tumor in whom the lesion was either not recognized or was ignored, or from meningitis resulting from faulty unsterile technique in performing the test. Both of these causes are largely avoidable and we have never seen a fatality in some 50 000 punctures done in private practice and clinic.

There is one unavoidable but fortunately very rare serious sequel of lumbar puncture namely subarachnoid hemorrhage following several hours later Among our own material we have seen a half dozen such accidents The hemorrhage is, curiously enough usually basilar and because of the superficial course of the nerves supplying the muscles of the eye often causes extraocular muscle palsies, even complete ophthalmoplegia. We have seen a patient with partial optic atrophy non progressive over a period of 6 years, in whom the lesion was probably produced by this cause With the vascular accident there may be headache slight fever but rarely coma and recovery is usually prompt and complete. There is no tendency for such reactions to occur especially in hypertensive patients indeed in the several examples we have seen hypertension was conspicuous by its absence It is however almost always found to occur in patients who are definitely neurosyphilitic, and is assumed to be due to a hemorrhage from a vessel weakened by syphilitic endarteritis.

Recently Pease has reported a series of cases which within a few days to two weeks after lumbar puncture developed pain in the puncture site, limitation of motion of the lumbar spine weakness of the back muscles, and in some instances difficulty in walking with pain referred down the thighs. In all his cases he was able to demonstrate narrowing of the inter vertebral space opposite the site of puncture as a result of pushing the needle into the intervertebral disc and the subsequent extrusion of the nucleus pulposus into the neural canal. We have never encountered or at least have never recognized, such a sequela to lumbar puncture. It obviously can be avoided by very careful manipulation of the needle after it has penetrated the dura. Should this complication occur expert orthopedic consultation and advice are necessary

Lumbar puncture headache —The only disagreeable feature of lumbar puncture is the occurrence of post-puncture headache. This type of headache differs from other forms of cephalalgia in that it disappears as soon as the patient lies down and reappears as soon as he assumes the erect position. In an ambulatory patient, it may develop 3–6 hours after puncture, is very severe (worse than any other headache we have ever seen except that of brain tumor or osteitis of the skull and so bad that even the most stalwart soul is forced to bed) and may be associated with vertigo, nausea and vomiting It is not relieved by drugs but disappears promptly in the recumbent position. For a day or two perhaps even for 2–3 weeks, it may recur, with gradually diminishing intensity as soon as the patient tries to get up. It is thought to be due to constant leakage of fluid through the puncture wound in the inelastic dura (Nelson)

Such headaches occur in about half the patients in whom puncture is performed in office or clinic, and who are allowed to get up and go home immediately or within a few hours. Curiously, they are much more liable to occur in individuals with normal nervous systems than in those with neurosyphilis. Many tabetics and paretics are completely immune, for reasons not understood. Post-puncture headache may be almost completely obviated by two simple precautions —(1) by utilizing a small needle, 20 to 23 gauge,* so that the puncture wound in the dura is small (2) by performing the puncture with the patient in the horizontal position in bed and by keeping him there, flat, without lifting his head off the pillow, for 48 hours after For the first 2–3 hours after puncture, he should lie on his face, so as to prevent drainage through the dural wound and to permit the formation of the delicate fibrin clot which closes it. Thereafter he may lie on side, back or face as he chooses provided only that he does not sit up This necessitates the use of a bed pan and of attendance at meal times, both of which are more readily supplied in a hospital than at home. With these precautions puncture headache is a comparative rarity in our experience.

When for any reason the patient cannot enter a hospital, the test may be made in office or clinic and the patient instructed to go home to bed at

* We have used the 23 gauge Green needle with rounded point, but find it too flexible and so small as to necessitate syringe withdrawal of fluid. We prefer a 20–22 gauge standard stainless steel needle, with medium bevelled point.

once. Under these circumstances the incidence of headache is increased. If it develops no treatment except bed rest and reassurance is of much avail. Efforts to increase intracranial pressure as by the use of pituitrin, the intravenous injection of sterile distilled water or forced fluids by mouth, are of little help.* The patient should be told that while the reaction is uncomfortable and annoying, it is not serious, and that with bed rest for an additional 24–48 hours it will probably disappear completely.

In our own clinic, lumbar puncture is performed routinely on ambulatory patients and a total of about 50 000 such tests have now been made. The inconvenience and discomfort of post-puncture headache are more than compensated for by the information gained by spinal fluid study so essential from standpoints of diagnosis, prognosis and treatment.

The technique of lumbar puncture.—In many clinics an elaborate operating room ritual, requiring the use of rubber gloves, sterile gowns, masks, etc., has surrounded the procedure of lumbar puncture with wholly unnecessary difficulties. We shall describe very briefly the technique employed in the Syphilis Clinic of the Johns Hopkins Hospital.

The position of the patient.—Almost the whole trick of lumbar puncture is the proper position of the patient. If this is correct, the rest is comparatively easy. For the inexpert, the sitting position is best, since landmarks are more easily located. The patient may straddle a straight backed chair, place his arms crosswise on its top, arch out his back and lean his head on his folded arms. For the adept, the lateral position in bed is advisable, since the risk of headache is minimized. The patient lies on either side, brings hips and shoulders both to the extreme edge of the bed, flexes his thighs, with knees bent up as far as possible toward his chin, and bends his head down toward his knees. This arches his back without conscious effort on his part and keeps the plane of the back perpendicular to the plane of the bed. A lumbar puncture board is unnecessary unless the bed is unusually sagging.

The interspace selected is the fourth or fifth lumbar. The fourth is directly opposite the iliac crests, the fifth next below the crests. The cord splits up into the cauda equina at the level of the first lumbar so that there is no danger of injury to it.

The performance of the puncture.—While the patient is being placed in position by an assistant and the skin sterilized with tincture of iodine followed by 70 per cent alcohol, the operator is scrubbing his hands thoroughly with a nail brush and green soap, after which the hands are rinsed in alcohol. Rubber gloves, sterile gown, etc. are unnecessary. The operator then drapes a sterile towel about or across the hips so that he may feel for the iliac crest without soiling his hands. The skin is anesthetized either with 0.5–2.0 per cent procaine injected intradermally or by freezing with ethyl chloride. The operator takes the sterile lumbar puncture needle by the butt, being careful not to touch it within an inch of the point, and

* Nelson suggests the prevention of leakage by insertion through the needle into the dural hole of pieces of catgut 3 cm. long. Since this procedure increases the risk of infection and since headache is almost completely preventable by bed rest for 48 hours, we believe it is inadvisable.

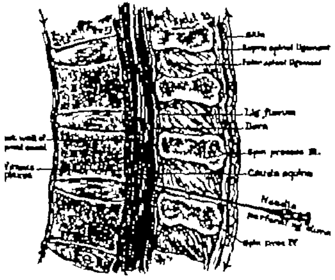


Fig. 14a.—Correct position of patient, lateral view spine flexed forward. Note separation of spinous processes, widening of posterior portion of interspace, position of needle slipping smoothly over upper border of lower spinous process.

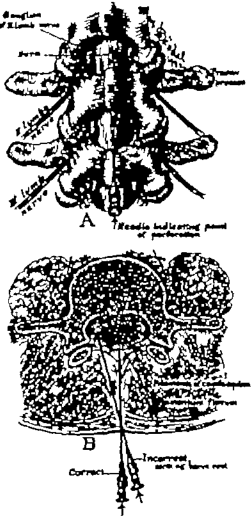


Fig. 14c.—Posterior view (A) and transverse section (B) back properly flexed. Note that needle introduced in midline meets no obstruction. If too far to one side, dorsal nerve root is struck, no fluid is obtained, and patient develops pain or "electric shock" in leg or foot of appropriate side.

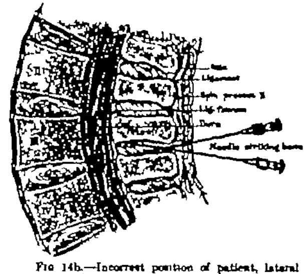


Fig 14b.—Incorrect position of patient, lateral view spine hyperextended and arched forward. Note difficulty, sometimes practical impossibility of introducing needle without striking bone.

Fig. 14.—The Technique of Lumbar Puncture

These semi-diagrammatic drawings show the correct route of the needle and the various structures through which it passes (a) skin, which is loosely fixed on underlying tissues, so that forcing the needle through causes it to slip up down, or to one side After the skin is penetrated, readjust the position of the needle point to the midline and the upper border of the lower spinous process; (b) the firmly fixed supraspinal ligament. After the needle has passed this point, its direction is difficult to alter (c) if directly in the midline, loose areolar tissue between the lumbar muscle *groups* if too far to one side, more resistant muscle must be penetrated, the contraction of which may throw the needle off direction (d) the ligamentum flavum. When this is met, a definite sense of resistance is felt; (e) just beyond the ligamentum flavum (1–3 mm.) the dura. This is a stiff inelastic membrane, which is usually entered with a distinctly palpable click (f) the subarachnoid space with filaments of the cauda floating in a bath of spinal fluid (g) if the needle is pushed too far a venous plexus on the anterior wall of the canal, accounting for bloody fluid.

The stylet should be withdrawn at the first sense of resistance (the ligamentum flavum) If no fluid is obtained, reinsert stylet, push needle on 1 2 mm withdraw stylet again, and repeat the procedure until fluid flows freely or bony resistance is encountered.

partially removes the stylet to make sure that it is not rusted into the shaft.

Within the selected interspace, the proper landmark is the *upper border of the lower vertebra*. The needle is introduced exactly in the midline, directed at an upward angle toward the head of about 10–15 The diagrams of Fig 14 clarify the course of the needle with varying positions of the patient indicate how easily the needle slips forward without meeting any bony obstruction if the patient s position is correct, and how impossible puncture may be if the patient s back is arched forward instead of backward. If the puncture is neatly performed, there is little or no pain. The periosteum is very sensitive however and a careless operator who scrapes over or attempts to push by bone may cause real agony There is no danger of injuring the cauda if one of its filaments is struck, it is pushed aside in its bath of spinal fluid.

If an obstruction is met with the patient in the proper position, or if the patient complains of pain or electric shock in the foot or leg, the direction of the needle is faulty either vertically or laterally It should be withdrawn past the superficial fascia and redirected. Rarely it may be necessary to withdraw completely and to use the adjacent interspace but under no circumstances should a patient be subjected to more than two unsuccessful attempts at lumbar puncture at a single sitting. It is better to postpone the effort until another day when a more expert operator should be called in.

The withdrawal of fluid —About 6–10 cc. of fluid is desirable for laboratory testing The flow may be expedited by jugular compression carried out by an assistant. This is especially desirable in a nervous patient. The fluid should be taken in three tubes the last of which contains only a few drops for an immediate cell count. A bloody fluid is valueless for all tests except the Wassermann though it may be used for this purpose if only blood tinged. If bloody fluid appears, a clear fluid may often be obtained by an exceptionally rapid and skillful operator by means of a second puncture one or two interspaces above but the average physician had better wait two weeks for all traces of blood to disappear before repeating the test

Except in the rare case of complete spinal block there is no such thing as a dry tap Failure to obtain fluid is due to faulty technique.

The care of needles Breakage of a needle in the patient — The best lumbar puncture needles are made of stainless steel. Even these will corrode with lack of care. After use, the needle should be washed dried out by passage through the shaft of alcohol and ether and a drop of white oil placed in the shaft before the stylet is inserted. Before boiling, they should always be tested for tensile strength, *with the stylet out*, by bending point and hub between the fingers.

Even with these precautions a sudden unexpected movement on the part of the patient sometimes causes a needle to break after it has been introduced. If the stylet is still in this is not serious, if the physician keeps his head. Withdrawing the needle slowly with simultaneous lateral pressure on the stylet hub will usually bring the broken piece out If not, and

if it is close to the surface, it may be grasped with sterile forceps through a small nick in the skin. If this is impossible, the patient should be transferred to the operating room and the needle surgically removed under fluoroscopic control.

Cisterna Puncture

Puncture of the cisterna magna, instead of the lumbar sac, is now used routinely in some clinics. It has two distinct advantages over lumbar puncture —(1) it is not followed by post-puncture headache, even though the patient remains upright afterwards and (2) medicaments introduced intracisternally are in much closer apposition to the base of the brain than when given intraspinally The absence of headache after cisterna puncture, as yet not satisfactorily explained makes it possible to utilize this method in ambulatory patients whose work need not be interfered with.

On the other hand, the method is distinctly more dangerous than lumbar puncture. Two serious or fatal reactions occur in every thousand patients, according to Weissenbach. We have seen a case of serious intracranial hemorrhage (reported by Dandy) due to the accidental puncture of an anomalous artery If the needle goes too far laterally it may puncture a vertebral artery if too far forward, the medulla may be entered, in either case with fatal results. Personally we do not favor the use of cisterna puncture except in the hands of an expert, and then only for treatment, not for routine diagnostic purposes. It is justifiable to take some risk in the treatment of a patient with optic atrophy for example but it is wholly indefensible to run a similar risk in a patient with uncomplicated early or latent syphilis.*

We paraphrase the technique of cisterna puncture as described by Ayer and Spiegel for the benefit of those who may wish to familiarize themselves with the method. Experience should always be gained on the cadaver before this procedure is attempted in the living patient.

The hair at the base of the neck should be shaved. The skin is sterilized as for lumbar puncture with tincture of iodine followed by alcohol. The patient lies on either side, the head flexed and supported on a small hard pillow It is important that the head does not tilt to either side, so that the spine and skull are in straight alignment. The palpable landmarks are the occipital protuberance and the axis Ethyl chlorid is a preferable anesthetic to procaine, since it does not obliterate the landmarks.

A special needle with a metal guard (Spiegel needle) is inserted directly in the midline about 0 5 cm. above the axis, and with a marked upward angle (Fig. 15) The needle is pushed forward and upward with the deliberate intention of striking the posterior lower edge of the occipital bone (edge of the foramen magnum) It is essential to strike this bone, since otherwise one may go too far with grave risk of injury to the medulla. When bony resistance is felt the needle is withdrawn slightly the hub elevated a little, and the needle reinserted for a distance of 0.5–1.5 cm.

* This opinion is shared by such workers as Cannon, Rosen, and Cornwall, among many others.

Study of the Cause and Prevention Arch. Dermat. & Syph. 21 615, 1930 — Pease, C. N Injuries to the Vertebrae and Intervertebral Disks Following Lumbar Puncture Am. J Dis. Child. 49 849 1935.—Saunders, H. C. and Spiegel, L.: Cisternal and Lumbar Puncture A Comparative Study of the Fluids in Syphilis J.A.M.A. 91 630 1928.—Spiegel, L. (a) Cisternal (Suboccipital) Puncture as a Routine Diagnostic Test in Preference to Lumbar Puncture, Med. J & Rec. 127 411 1928. (b) Further Observations on Cisternal (Suboccipital) Puncture New York State J Med 29 945 1929 —Weissenbach, R. J., Bocage A., and Block Michel, H. Hémorrhagie méningée au cours d une ponction sous-occipitale Bull. Soc. franç de Dermat. et Syph. 42 785, 1935.—Wieder L. M : A Study of Ill Effects from Lumbar Puncture with Report of a Postpuncture Fatality Am. J M. Sc. 173 854 1927

to complete the necessary period of medical care under the facilities of private practice or pay or free clinics Methods of treatment must sometimes be adjusted to the patient s ability to pay for them. The probable cost should be weighed against the question of therapeutic advantage.

If the patient is married, he should be strongly advised to be frank with his marital partner who must of necessity be examined, not only because of the possibility of transmitted infection, but also from the standpoint of protection of the patient himself This question is discussed in more detail in Chapter XXX. *Knowledge of the existence of a syphilitic infection,* even if recently acquired, can be conveyed to the average marital partner without disclosing the act of sexual indiscretion on the part of the patient. The opportunities for extragenital and accidental infection are sufficiently great that neither the physician nor the patient need unduly emphasize the exact circumstances under which the infection was acquired.

The general medical care of patients with early syphilis — From the general medical standpoint, the average patient with an early syphilitic infection is fortunately young and aside from the lesions caused by syphilis in good general physical condition. In most instances we do not believe that any general medical advice is necessary except one major precaution avoid excess in all things. Nothing is gained we believe, by special diets, whether or not calculated as with certain recommended high carbohydrate or high fat diets to reduce arsphenamine toxicity Nothing is gained by the complete prohibition of alcohol. There is no advantage secured in prohibiting the use of tobacco (except by chewing) unless it is used to great excess. It is currently stated in most modern texts that the use of tobacco predisposes to the recurrence of infectious lesions on the buccal mucosa and to intolerance to bismuth and mercury In an experience covering many thousand patients we have seen nothing to indicate that these are facts. We think drinking or smoking in moderation do no harm It should however be insisted that the patient lead a reasonably hygienic life that he obtain some outdoor exercise and adequate sleep

It is quite unnecessary for the average patient with early syphilis to abandon or change his occupation because of his infection unless he is a food-handler or engaged in some other duty such as that of child s nurse involving close physical contact with other individuals. Even in this case, a temporary lay-off during the first 2 weeks of arsphenamine therapy eliminates the relatively remote danger of infection of others by the average indirect physical contacts of daily life (provided, of course that treatment is regularly continued) It is also unnecessary and we believe undesirable to hospitalize and isolate a patient with early syphilis unless as rarely occurs, he is actually ill as a result of the constitutional reactions accompanying his early infection. Even then he may be discharged from the hospital and permitted to return to his usual duties within a few days after the subsidence of symptoms

It is most unwise to cause the average syphilitic patient to regard himself as socially outcast and pariah by the prohibition of most of the simple pleasures of life He does not endanger himself by living a normally hygienic existence *his danger to others,* while he is under treatment, lies

almost entirely within the close physical relationship of sexual indulgence, which must be discussed in more detail.

The control of infectiousness in early syphilis (see Chapter III) —Reduction of the incidence of syphilitic infection in the general population depends mainly on two factors both of which are largely within the control of physicians. These are, first, the early recognition and adequate treatment of early syphilis to the point of non infectiousness and second, the prevention of the spread of the infection by the patient by means of some advice as to restriction of intimate physical contact with others. The first of these points is so important that it will be separately considered in the next chapter in a discussion of the duration of antisyphilitic treatment.

The recently infected patient with syphilis is usually anxious to know how soon he may resume sexual relations. We lay stress on this point whether or not the patient is married inasmuch as most individuals with early syphilis, married or single, are sexually active. The mechanism of infectiousness by moist lesions on mouth or genitalia, and the unlikelihood of infection of others by any relationship not involving direct or close indirect contact of buccal or genital surfaces, should be explained to the patient. The treponeme is viable when moist, it dies as soon as it dries. It should be explained to the patient that although in most instances surface organisms are destroyed and lesions healed with the first few weeks of treatment, the possibility of infectious relapse within the first six months, even during treatment, cannot be entirely ruled out and that semen may be infectious. Sexual intercourse and kissing should be advised against during the first six months of treatment, unless of course the sex partner is already infected, in which case restrictions are unnecessary. Following this period of time and provided the patient is still under active treatment, kissing may be resumed, although it should be limited to more or less platonic salutes on the cheeks rather than to moist contact of the lips. Sexual intercourse may also be resumed if two conditions are fulfilled: first, that the patient wears a condom * and second that intercourse is permitted only during the arsenical phase of therapy. Unrestricted sexual intercourse with the resulting possibility of pregnancy should under no circumstances be permitted until the patient has completed not only antisyphilitic treatment, but also a full year of post-treatment observation, during which he satisfies the conditions outlined in a subsequent paragraph on the criteria of cure. The reason for this seemingly rigorous restriction is the possibility that the sex partner may be infected by means of macroscopically invisible mucosal lesions, or less probably by semen even in the absence of noticeable moist lesions in the patient.

The patient must also be warned against indirect contacts, for example he must not allow himself to leave about objects which he has had in his mouth, such as pencils, cigarette holders, cigar holders, pipe and eating utensils. There is some danger that a non-infected individual may pick up such an object, still moist with the patient's saliva, and place it in his

* In the case of a female patient, her uninfected sex partner should protect himself by the use of a condom. Preliminary sex play should be strictly avoided.

own mouth. Dry objects are not dangerous For the first two or three weeks of treatment, table silver plates, cups and glasses should be boiled after using Later than this only ordinary cleanliness is necessary The patient should sleep alone. We have seen several instances of infection of young brothers and sisters who slept in the same bed with an infected individual even though sexual contact and kissing is said not to have taken place It is desirable that the patient have his own towels, wash cloths, sponges, etc. in the bathroom Soap is treponemicidal and infection from it need not be feared.

The local treatment of early syphilis —It seems hardly necessary to repeat that excision of the chancre, with the hope of aborting syphilitic infection is useless. Treponemes have been distributed throughout the body days before the chancre appears, and nothing whatever is gained by ablating the lesion. Except in the case of phagedenic chancre, due to mixed infection the local treatment of the primary lesion or early cutaneous or mucosal lesions is entirely unnecessary Surface treponemes are destroyed within a few hours by the injection of an arsphenamine, and the lesions of early syphilis heal within a few days. Nothing is gained by antiseptic applications soap and water cleanliness is all that is necessary

In the case of phagedenic chancre, the best form of local treatment is that advocated by Cole for chancroid. The cautery and caustics should be avoided as tending to sear the top of the area, the infection proceeding beneath. Cleanliness and the use of soothing non-irritating applications, such *as hot boric acid or hot potassium permanganate soaks* (1 8000–10000) are advised. Dry heat, such as may be obtained by exposing the lesion to a large electric light bulb under a tent for several hours daily promotes rapid healing. Powdered iodoform or sulfanilamide may be dusted on the lesion. If the major involvement is on or under a phimotic prepuce, the patient may be circumcised but only if he can be placed in bed in the hospital.

If suppurating inguinal adenitis develops as a result of the secondary infection of a chancre the patient should be placed at rest in bed A small nick is made over a fluctuant area of the bubo, the pus gently expressed and a pressure bandage applied over the groin. After 24 hours the bandage is removed, the cavity evacuated by pressure, and with a Record syringe, 1–2 cc. of an antiseptic solution* is injected into the gland cavity and allowed to remain for one minute. A needle is not necessary the nozzle of the syringe being forced into the small opening made the day before, and the elbow of the syringe pressed against the skin in order to prevent the escape of fluid. Alternatively the abscess cavity may be filled with powdered sulfanilamide. Following this procedure, a pressure bandage is reapplied for 48 hours. The legs must not be flexed but should be kept extended in order to keep heavy pressure over the area. The injection of the antiseptic solution or sulfanilamide may be once or twice repeated (not oftener than every three days) if pus continues to discharge, but in the majority of cases a single injection suffices This method of local treatment

* Composed of iodoform, guaiacol, eucalyptol, and 95 per cent alcohol, each 10 grams or cc. balsam of Peru, 30 cc. ether 100 cc.

has proved itself far superior to the more customary incision and drainage, with its prolonged convalescence and secondary infection of the incised wound (Cole)

The single exception to the omission of local treatment in early syphilis has to do with the relatively common eye lesion of iritis or uveitis. Here a 1 per cent atropin solution should be instilled into the affected eye and dilation of the pupil maintained in order to prevent adhesions between iris and the anterior capsule of the lens, until the inflammatory lesion has completely resolved (see Chapter XX)

The aim of treatment in early syphilis —The aim of treatment in early syphilis is the complete eradication of the syphilitic infection and the "cure" of the patient. This is quite unlike the situation in late syphilis where in most instances the best that can be accomplished is the amelioration of symptoms and the arrest of progress of the disease. A subsidiary aim of treatment is the control of infectiousness. Considering the importance of the objects to be accomplished the type of treatment to be given should be the maximum amount consistent with the safety of the patient. Minor treatment reactions may be disregarded and the patient urged to put up with their inconvenience for the sake of the desired result.

The criteria of "cure" in early syphilis —As we have already pointed out (Chapter II) reinfection though generally accepted as the only definite evidence of "cure" of syphilis in man is hardly a valid criterion, if judged by the results of controlled experiments in animals. It is possible that an individual in whom infection persists may be superinfected likewise that he may be refractory to reinoculation even though the first infection has been completely eradicated.

It is, however generally assumed that if a patient is reinfected, he has been "cured" of his first infection. It is perfectly possible to make one's criteria of reinfection so rigid that no case will fit the rules. Halley and Wasserman, who have reported the reinfections from our own clinic and who at the same time surveyed the literature, found that only 229 of 676 reported cases in the literature were acceptable as reinfections on the basis of two simple criteria, as follows —

1 "There must be proof that the patient had syphilis prior to the occurrence of the suspected second infection, and this proof must rest on the demonstration of spirochetes in a lesion or the occurrence of a positive blood Wassermann reaction in the blood serum, and not on clinical judgment alone.

2 "After an interval following antisyphilitic treatment and at a site other than that of the primary lesion of the first infection there must develop a lesion with the characteristics of a chancre in which spirochetes can be demonstrated.

Stokes has summarized the requirements for proof of reinfection in three groups indisputable probable and possible. In the very large material of the C C G he was able to find none that was indisputable according to his criteria, which are however so rigid and numerous that the identification of a case as reinfection on the basis of these requirements would be almost impossible on the basis of the laws of chance We cannot entirely adhere to

the very strict standards set up by Stokes and feel that a patient may be regarded as reinfected if he fulfills the two criteria mentioned by Halley and Wasserman and one additional requirement, as follows

3 That at the time of the supposed second infection the serologic test is negative and that while under observation and during a period in which treatment is purposely withheld, the serologic test becomes positive or the patient develops outspoken secondary syphilis.

The great rarity of reinfection in man is illustrated by the fact that out of the more than 6 000 patients with early syphilis of the C.C G , only 31 were subsequently observed with a probable second infection. Reinfection is not applicable as a criterion of cure to patients with late syphilis, in whom this phenomenon does not occur Halley and Wasserman were able to find in the literature only 4 examples of supposed second infections in individuals in whom treatment was begun after the period of early syphilis had been passed.

Lymph node transfer which is an acceptable method of the demonstration of the persistence of infection in the experimental animal particularly in the rabbit, is not applicable to man. The studies of Lake and his associates have shown that in a considerable number of patients with untreated late syphilis the transfers of lymph nodes to experimental animals was not productive of infection. Since lymph node transfers may be negative in patients with known active syphilis, the method can be of no value in determining the fact of cure. Tissue transfer of other organs than lymph nodes is obviously not applicable to man.

A possible method of determining the persistence or absence of infection in treated human patients is by means of necropsy evidence Careful studies of this nature are almost completely lacking from the literature. Warthin s work is not applicable, since he fails to supply any data as to the amount of treatment his presumably cured patients had received before death. The lack of detailed necropsy studies of adequately treated and clinically cured patients with early syphilis constitutes the greatest hiatus in our knowledge of the pathology of syphilis Every effort should be made to obtain necropsies on such patients who have subsequently died from any cause Even with the most searching pathologic study however it is easier to make a positive than a negative diagnosis. To assure oneself of the complete absence of the treponeme from the body is an undertaking which as Krause has suggested for the analogous problem in tuberculosis would require the serial sectioning or the inoculation into animals of every structure in the body

The luetin test or its more recent modifications is of no value as evidence either of the presence of syphilitic infection or of its cure. These are non-specific tests, often negative in patients with active syphilis and often positive in non-syphilitic individuals, in whom the reaction may be brought out by such non-specific means as the simultaneous administration of potassium iodide.

The so-called provocative serologic test is also of no value as a method of determination of the fact of cure As will be subsequently pointed out

(Chapter XXVIII) there is grave doubt as to the genuine existence of a provocative serologic test in syphilis under any circumstances.

Inasmuch as there is as yet no definite single test which can be applied to determine the fact of "cure" it is necessary to fall back on prolonged clinical observation. The real test of "cure" is the fact that the patient remains free of clinical or serologic signs of syphilis, and that he does not infect others. Many syphilologists have hesitated to carry this idea to its logical conclusion, which is that *no syphilitic patient should ever be discharged as permanently "cured."* If the definite requirements outlined for a post treatment year of probation are satisfactorily completed (pp 228–229), the patient is probably "cured," i.e. the percentage chance of a possible subsequent relapse is presumably not greater than 5 to 10 per cent. In order to guard against the possibility of such a subsequent relapse, which incidentally is more to be feared in the cardiovascular apparatus than elsewhere, periodic physical and serologic examinations should be carried out at intervals for the balance of the patient's life.

The patient's first question, once he has recovered from the shock of learning the diagnosis, is "Doctor can I be cured?" What shall he be told? We believe that complete frankness is desirable. The observant reader will have noted that wherever the word "cure" has been used in this discussion it is enclosed within quotation marks. It is in this sense that it should be used to the patient. It is, of course, wise and even essential to stress the fact that, given cooperation in treatment, there are 19 chances out of 20 of a favorable outcome and only one chance in 20 of progression. That one chance, however justifies emphasis on the point of view that for the patient the price of the maintenance of good health is eternal vigilance. The periodic examinations for a life-time should, if properly carried out, detect the development of possible progression before grave and irreparable damage has occurred which may in most instances be prevented by appropriate further treatment their inconvenience and expense are a small price to pay for protection against crippling relapse or death from syphilis. To tell a patient with early syphilis in definite terms that he is "cured" and that he need never return for further observation, may result in most embarrassing repercussions for the physician and in disaster for the patient himself or for his family in the form of subsequent progression or the infection of innocent persons. (See Chapter III for a more detailed discussion of this important problem.)

A discussion of contingencies which may arise during post-treatment observation and of their management is reserved for the greater detail of Chapter XIII

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CHAPTER XIII

THE TREATMENT OF EARLY SYPHILIS

The Development of a Plan of Treatment, and the Results Obtainable from It

A FUNDAMENTAL difference in considering methods of treatment for early and for late syphilis is that in the former general principles applicable to most patients may be formulated with much greater ease than in the latter To overstate the point, in early syphilis one may treat the disease, in late syphilis one must treat the patient. Most patients with early syphilis are healthy young adults, who are, except for the lesions of syphilis in excellent general physical condition. They are free from degenerative diseases of advancing years, so common in older patients with late syphilis and even the lesions of syphilis themselves have not as yet caused, in most instances, anatomic and physiologic damage to vital structures. Moreover the distribution of organisms in the tissues, the lesions they cause and the immunity response they provoke, are strikingly alike in patients with early syphilis, in contrast to the varied localization of destructive or fibrotic lesions and the probably equally varied immune states in patients with late syphilis.

For these reasons the formulation of a plan of treatment for early syphilis permits less consideration of the individual patient and more of the biologic course of syphilitic infection and of the chemotherapeutic properties of antisyphilitic drugs. The method of treatment to be presented was formulated in its major features by Keidel twenty five years ago, on the basis of such reasoning, and has since been subjected to minor modifications as added experience seemed to demand them As the various elements of the plan are discussed, they will be illustrated by the actual results of treatment, drawn largely from our own clinical material and from that of the C C.G

The ultimate results of treatment of early syphilis —The ultimate results of treatment for early syphilis, regardless of the factors of duration and amount, the time after infection it was instituted, etc are shown in Fig. 16. These are drawn from Padget's study of the Johns Hopkins material a study which is of major importance since it is the first in the literature with really adequate long-term observation of treated patients. All patients* included in this compilation were followed for a period of at least 5 years after termination of treatment. As shown, 65.7 per cent were cured, regardless of the type or amount of treatment given, in the sense that they either experienced reinfection or at the time of their last examination showed no physical or serologic evidence of syphilis. Of the remainder positive serologic tests were the only evidence of infec-

* The inclusion among these 551 patients of 17 who received no treatment for early syphilis does not materially influence the results of this analysis.

tion in 14 9 per cent 12.3 per cent had neurosyphilis, and 7 1 per cent various late manifestations of the disease other than neurosyphilis Even if one excludes from the 'cured group the patients in whom no examination of the spinal fluid was performed (8 7 per cent) the percentage of ultimate satisfactory outcome (57 0 per cent) is surprisingly high. This means that regardless of all other circumstances except that he received some treat

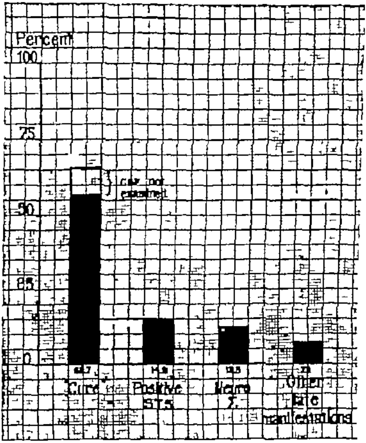


Fig 16 —Final outcome regardless of other factors in 551 patients with early syphilis (Padget)

ment during the first two years of his infection the patient with early syphilis has better than an even chance of becoming and remaining clinically and serologically well. The factors which influence the success of treatment will be shown presently

The relationship of early diagnosis to success in treatment — The time after infection at which the diagnosis of early syphilis is made and treatment instituted is of major importance in the ultimate outcome. The cure of early syphilis is much more readily obtainable when treatment is begun within the first few days of the infection than when it is delayed until the appearance of a positive serologic test or of outspoken secondary

manifestations. This is illustrated by Fig. 17 Leaving out of consideration for the moment the total amount of treatment and the manner of its administration, and including both cooperative and uncooperative patients, the probability of "cure is at least some 26 per cent better in seronegative primary than in seropositive primary syphilis, and 14 per cent better than after the appearance of secondary lesions. This means literally that the delay of a few days in arriving at a diagnosis of early syphilis may decrease the patient's chance of a favorable outcome by 15 to 20 per cent. With a comparable series of cooperative patients, therefore, to each of whom is given the maximum of desirable treatment, better results than those shown are obtained in all groups. However the same relative differences, according to the duration of infection at the time treatment was begun prevail. With the best available present-day treatment, the chances of cure" in seronegative primary syphilis are approximately 100 per cent, in seropositive primary syphilis 90 per cent, and in early secondary syphilis 90–95 per cent. The insistence of modern syphilologists on the early diagnosis of syphilis is thus thoroughly justified. The requisite speed in the diagnosis of primary syphilis implies intelligent use of the darkfield microscope.

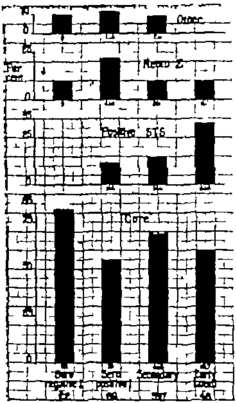


FIG. 17 —Influence on the final outcome of the stage of syphilis at the onset of treatment (Padget)

The data of Fig. 17 show an additional point of interest. The incidence of asymptomatic neurosyphilis is higher all other factors being equal in seropositive primary syphilis (21.8 per cent) than in early secondary syphilis (8.8 per cent) This indicates, as suggested by Moore and Kemp and others, that resistance against infection is heightened by permitting the tissue reaction of secondary syphilis to occur This observation, however is of no practical importance since the public health aspects of syphilitic infection demand its immediate early treatment at whatever stage the diagnosis may be made.

Relapse in early syphilis its time relationship to treatment and its prognostic significance —The stage of the disease at the start of treatment has some influence on its tendency to relapse (Table 29) Interestingly enough, relapse is more frequent in adequately treated pa

tients with primary syphilis, whether seronegative or seropositive, than in patients who have developed frank secondary lesions before treatment. The increase of relapse in primary as opposed to early or delayed secondary syphilis is entirely due to an increase in the incidence of early infectious relapse. This is surely related to the extent of the development of the patient's own tissue defenses brought about by the evolution without treatment of secondary lesions. The tissue response to these lesions apparently decreases the probability of early infectious relapse, but the tissue damage done by the more extensive invasion of the treponemes into the nervous system aorta, etc., is productive of an increase in various late forms of progression or relapse.

TABLE 29

THE INCIDENCE OF OBSERVED RELAPSE IN ALL TYPES OF EARLY SYPHILIS[4]
(Data of C C.G.)

Type of early syphilis	Incidence of relapse		
	All types	Early infectious relapse	All other types
Seronegative primary	10.7	8.3	2.4
Seropositive primary	12.5	10.2	2.3
Early secondary	8.9	5.4	3.5
Delayed secondary	10.8	5.0	5.8

Based on 6,528 patients with early syphilis.

Most important, however is that early infectious relapse is early evidence of the inadequacy of treatment. Eighty-four per cent of relapses of this type occur within the first two years of infection. The average interval between the last treatment and the appearance of the relapse is 9 months. Within the first 6 months after treatment ceases, 45 per cent of these relapses occur *by the end of the first year 73 per cent and by the end of the* second year 91 per cent (cf pp 22–24)

Neurorecurrence, the analogue of early infectious relapse in the nervous system is also a relatively early phenomenon, which is considered in more detail in Chapter XXII. This lesion usually appears within the first 2–3 months after the cessation of inadequate treatment, but in contrast to mucocutaneous relapse, the average interval without treatment, prior to the development of the neurorelapse, is only 8 weeks.

The interval between treatment and other forms of relapse or progression is measured in years rather than in weeks or months. For benign late syphilis the average interval in our own material is 29 months for various types of late central nervous system syphilis it is 3 years for cardiovascular syphilis it is even longer 10 or more years. The interval between infection and the appearance of these late forms of relapse in skin bones, nervous system or cardiovascular apparatus, seems materially to be short-

ened by inadequate modern treatment. When early syphilis passes unrecognized or untreated the average interval between infection and the appearance of benign late cutaneous or osseous lesions or of meningovascular neurosyphilis is 3–7 years of tabes and paresis, 12–18 years and of cardiovascular syphilis, about 20 years.

The prognostic significance of relapse (Padget) is shown in Fig. 18. Among patients in whom it was known to have occurred, "cure" was three times less frequent than among those in whom it was not observed. In addition, neurosyphilis and the other manifestations of progression were both six times more frequent among those who had relapsed than among those who had not. The high incidence of neurosyphilis in the former group is partially explained by the frequency with which relapse consisted of early acute involvement of the nervous system (neurorecurrence) These observations point out not only the ominous prognostic significance of relapse in early syphilis, but serve to illustrate a point that will be emphasized frequently during this chapter—the successful outcome of early syphilis depends almost entirely upon regularity of treatment.

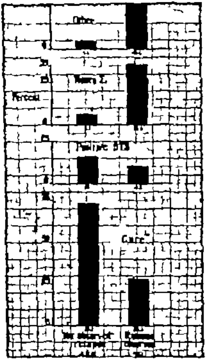


FIG. 18.—The prognostic significance of observed relapse (Padget)

The choice of drugs arsphenamine neoarsphenamine mapharsen.—The weapons which the physician commands are limited to a relatively few representatives of three drug groups, the arsenicals, the heavy metals, and the iodides. Among the arsenicals the choice at present lies, for all practical purposes, between four representatives arsphenamine, neoarsphenamine, silver arsphenamine, and mapharsen. Sulpharsphenamine is not to be considered because of its relatively high toxicity particularly in producing reactions of the dermatitis and blood dyscrasia groups (unless the complete absence of available veins necessitates the intramuscular administration of all drugs) bismarsen is out of the question because of its relatively low therapeutic efficiency * In Chapter VI, describing the

* We are aware of the high regard of some clinicians for bismarsen, and their feeling that the ultimate clinical outcome after its use is good, in spite of its relative inefficiency in destroying surface organisms, in healing lesions, and in serologic reversal. However we feel that the evidence as to ultimate clinical outcome is incomplete as yet, and that the disadvantages of bismarsen are such as to forbid its substitution for more powerful arsenicals in early syphilis unless this is absolutely essential for such a definite reason as the lack of available veins.

arsphenamines, evidence is provided both from experimental and clinical standpoints to indicate that old arsphenamine (606) is superior in early syphilis to other members of the group In human beings this superiority is manifest in the rate of disappearance of spirochetes from open lesions in the rapidity of healing of lesions, and in the rate of reversal of the serologic reaction. All these advantages, however are subsidiary to the main question Is arsphenamine productive of better clinical results in terms of percentage of cure than other arsenical drugs?

The material of the C C G presented in Table 30 indicates that this superiority also exists, at least as between arsphenamine and neoarsphenamine Based on a total of nearly 3 000 patients in whom the two drugs

TABLE 30

ARSPHENAMINE VERSUS NEOARSPHENAMINE IN EARLY SYPHILIS (2,689 CASES FOLLOWED FOR 6 MONTHS OR LONGER)

(Data of C.C.G)

Scheme of Treatment	Arsphenamine		Neoarsphenamine	
	Results satisfactory	Relapse (all forms) or serologic resistance	Results satisfactory	Relapse (all forms) or serologic resistance
Continuous	35 9	12 4	20 3	16 4
Intermittent	21 5	20 4	17 6	23 1
Irregular	13 1	45 1	14 3	46 7

Leaving out of consideration the total amount of treatment administered.

could be compared on the basis of various plans of treatment (the ideal of continuous, the less desirable intermittent, and the haphazard method of irregular treatment), the results seem definite. Omitting a consideration of the total amount of treatment administered, the superiority of arsphenamine over neoarsphenamine when the continuous method of treatment is used is apparent in terms of ultimate satisfactory outcome (35 as compared to 20 per cent) and of relapse or serologic resistance (12 as compared to 16 per cent) The differences between the two drugs tend to disappear when the continuous method is abandoned in favor of the less satisfactory intermittent or irregular schemes. With the former the advantage of arsphenamine is only slight with the latter it does not exist at all. In early syphilis, the chance of radical cure is so good that nothing less than the best methods of treatment should be utilized.*

Mapharsen —The rapidity with which mapharsen causes healing of the lesions of early syphilis and the reversal of serologic tests has been shown in Table 16 and Fig 25 Unfortunately there are as yet no long term studies with this drug in the treatment of early syphilis which permit

* Given an uncooperative patient, who refuses to carry out continuous treatment, the superiority of arsphenamine vanishes, and as much may be accomplished by the haphazard administration of neoarsphenamine as with the more powerful drug.

its accurate final evaluation and certainly none which even remotely lend themselves to comparison with the vast information accumulated concerning arsphenamine and neoarsphenamine. Although it causes the prompt disappearance of surface treponemes, the rapid healing of early lesions, and prompt serologic reversal, a single injection of mapharsen is excreted in 2–3 days in contrast to the 5–7 days required for arsphenamine or neoarsphenamine. Since it is desirable in the treatment of early syphilis to reach and continuously maintain a critical therapeutic blood and tissue concentration of all antisyphilitic agents, the administration of mapharsen at conventional weekly intervals may prove to be less satisfactory than a shorter interval of 4, 3, or even 2 days. The "rhythm" of treatment with this drug has not yet been adequately studied. If ultimately treatment with mapharsen oftener than once a week seems desirable this may prove to be a serious handicap in the clinic if not in the office, management of early syphilis.

It is, however, more difficult now (1941) than it was eight years ago when the first edition of this book was prepared, to be dogmatic as to the best arsenical drug for early syphilis or the best method of its use. While we still believe that arsphenamine is the most efficacious, it seems clear that mapharsen (and perhaps other arsenoxides to come) are preferable to neoarsphenamine in all respects. We confess to a mental reservation that perhaps mapharsen or one of its related products will finally prove to be superior to arsphenamine itself, when moot questions of dosage, interval between treatments, length of courses, and other factors have been more thoroughly studied. Our present opinion can best be summarized by saying that formerly the enforced substitution of neoarsphenamine for arsphenamine in the treatment of a given patient with early syphilis left us with a distinct feeling of regret, while now if mapharsen must be used, we feel that treatment may be so adjusted as to give a chance of cure almost, even if not yet quite, as good as with arsphenamine.

Certainly the arsphenamine arrow has practically disappeared from the syphilotherapist's quiver in all *except* early syphilis; neoarsphenamine is justly disappearing in early syphilis and is reserved for late syphilis alone; mapharsen or some other arsenoxide *may* take the place of both of them in early and late syphilis alike.

The syphilologist is thus caught on the horns of a dilemma. Shall he continue to advise the use of the technically difficult arsphenamine in place of the relatively simple neoarsphenamine or mapharsen,* even though he is faced by the fact that the practitioner tends to disregard his advice and to use the simpler preparations? Or shall he compromise with what he believes to be the best treatment available and attempt to plan an outline of therapy based on the use of the latter drugs? From our own point of view there can be only one answer. The demonstrated superiority of arsphenamine to neoarsphenamine in early syphilis, when the continuous plan of treatment is employed, is still so great that, in spite of the

* We do not include silver arsphenamine in the comparison because information adequate to establish its relative worth is not available and because its prolonged use (24 or more injections) in combination with bismuth raises the danger of argyria.

minor technical difficulties surrounding its preparation and administration it should be used whenever possible. Neoarsphenamine and possibly mapharsen, are distinctly second best. If they are used, it should be for other reasons than that they are less bother to give than arsphenamine. Circumstances will of course arise which demand the use of the simpler drugs, as for example the exigencies of rural practice, poor veins, a tendency on the part of the patient to reactivity after arsphenamine, etc. But these reasons should be good ones and not the inadequate reason of most physicians—that arsphenamine is too much trouble.

The dosage of the arsenical drugs in early syphilis —As to the dosage of the arsenical drugs to be given to the average patient with early syphilis, it must be kept in mind that maximum treponemicidal attack is desired from the outset. The initial dosage should not be small with gradual step-like increases until an average therapeutic dose is reached. By this system, there is theoretical and some practical danger of producing a drug-fast strain of organisms. On the contrary, it is wiser to give the first three injections at a dosage level of 0 1 gram of arsphenamine or 0.15 gram of neoarsphenamine for each 25 pounds of body weight, i.e., for a 150 pound man, 0 6 gram of arsphenamine or 0 9 gram of neoarsphenamine. These doses should not be exceeded, however, no matter what the body weight. The initial and subsequent doses of mapharsen in early syphilis should be the same in either sex, 0 060 gram (60 mgms) The chief *objection to large initial dosage is the fear of intensifying the constitutional* symptoms (chill fever and malaise) of the therapeutic shock (Herxheimer reaction) after the first injection. In our experience, however this reaction is as frequent and about as intense with small as with large initial dosage, and, while uncomfortable, is not dangerous and not alarming if the patient is forewarned.

After the first 3 injections have been given, the average therapeutic dose of arsphenamine is 0 4 gram for men and 0.3 gram for women of neoarsphenamine 0 75–0 9 gram for men, and 0 6–0 75 gram for women. We cannot agree with Schamberg's contention that the maximum dose of neoarsphenamine should not exceed 0.3–0 6 gram (or of arsphenamine, by analogy 0 1–0.3 gram) He advises this relatively low dosage on the ground that the incidence of serious reactions, particularly dermatitis, jaundice and encephalitis, is reduced and holds, although he produces no supporting facts that the results obtained in early syphilis with small doses are equal to those obtained with large doses. We believe both these assumptions to be unjustified. Serious reactions, i.e. jaundice and dermatitis, are in our hands more frequent after neoarsphenamine in any *dosage than after arsphenamine and equally as frequent after* small as after large doses of 914 Their greatly decreased incidence after mapharsen is a strong point in favor of the use of this drug. As for therapeutic efficiency the study of Oelze is of interest. He found that with doses of less than 0 6 gram neoarsphenamine, treponemes still persisted in surface lesions after two days in a considerable proportion of patients with early syphilis, and that even after 0 6 gram, organisms were present for 48 hours in 4 per cent of the patients studied. He concludes and we agree, that it is

necessary to use large doses to sterilize lesions and presumably also, therefore, to sterilize the patient.

Bismuth versus mercury —As is indicated in Chapters VIII and IX, in the experimental animal bismuth is distinctly superior to mercury in its curative power The therapeutic index of various bismuth preparations

TABLE 31

RELATIVE EFFICIENCY OF BISMUTH AND MERCURY IN EARLY SYPHILIS AS REFLECTED IN WASSERMANN REVERSAL

(Data of C.C.G)

Treatment		Total patients treated	Percentage showing serologic reversal within 12 months
Arsphenamine	plus bismuth	237	55 9
	plus mercury	466	44 7
Neoarsphenamine	plus bismuth	48	54 6
	plus mercury	65	46 8

Omitting consideration of the method (continuous, intermittent, etc.) by which treatment was given.

ranges from 1 to 166 that of any known mercury preparation is not greater than 2. Whether these marked differences in the experimental animal are directly translatable to human syphilis is not as yet definitely known. A direct comparative evaluation of the two drugs in the human being is difficult because of the fact that neither of them is used alone but only in conjunction with an arsenical. The studies of the C C G provide evidence to show that in early syphilis, bismuth is slightly but

TABLE 32

RELATIVE EFFICIENCY OF BISMUTH AND MERCURY IN EARLY SYPHILIS AS REFLECTED IN THE INCIDENCE OF INFECTIOUS RELAPSE

(Data of C.C.G.)

Treatment	Total patients treated	Percentage Incidence of Infectious Relapse
Arsphenamine plus bismuth	603	3 6
Arsphenamine plus mercury	1117	9 8

Omitting consideration of the method or total amount of treatment.

definitely superior to mercury as regards its influence on serologic response and on the incidence of infectious relapse. Used in conjunction either with arsphenamine or neoarsphenamine, serologic reversal is secured within 12 months in 55 per cent of bismuth treated patients, as compared with 44–46 per cent in those treated with an arsphenamine plus mercury In-

fectious relapse is more than twice as common in patients treated with arsphenamine-mercury as in those treated with arsphenamine-bismuth. These differences are however, only slight. No definite information as to possible differences in the percentage of ultimate 'cure' is as yet available Certain other studies, such as that of Harrison have seemed to indicate that there is very little real choice between the two drugs in the treatment of human beings Bismuth has one real advantage over mercury there is much less risk of immediate or cumulative toxic effect. The best *method of administration of mercury in our opinion, is by inunction.* The much cleaner and less time-consuming method of the intramuscular injection of insoluble bismuth salts together with the definite superiority of bismuth in the experimental animal and the indications of its superiority *however slight,* in the human being *seem to point to the choice of this* drug rather than mercury in early syphilis. It may be worth while since the mechanism of the therapeutic action of the two drugs may differ to use both at some time during treatment. And when the economic status of the patient necessitates some reduction in the cost of treatment, the less expensive inunction of mercury may be substituted for bismuth without much sacrifice of therapeutic efficiency

The iodides —The iodides may be given empirically to every patient with early syphilis at some period during treatment, usually in association with a heavy metal There is no definite evidence that they are of any value in this stage of the infection. They are often so utilized because of their known effect on late granulomatous lesions in which they certainly enhance the resolution of lesions and possibly therefore penetrability of the treponemicidal arsphenamines and bismuth preparations. Under these circumstances it is at least conceivable that they may aid in the penetration of such lesions, if any exist, in early syphilis

The choice of a system of treatment —Abortive treatment — Until the advent of the so-called five-day' treatment of early syphilis using massive doses of an arsenical by continuous intravenous drip (to be separately discussed in Chapter XXXIII) it has been generally agreed that abortive" treatment by any system of compressing greatly intensified dosage into the early days or weeks of therapy was a complete failure. The "five-day" system has, however re-opened the subject in a manner which requires more detailed and special consideration. Nevertheless since these newer treatment systems are still (July 1941) wholly experimental in character, it seems to us wise to proceed with a detailed discussion of standard treatment methods which will certainly be in general use for many more years

Simultaneous or separate administration of arsenicals and heavy metals —Having arrived at the decision to use arsphenamine or mapharsen in preference to other arsenical drugs, and intramuscular injections of an insoluble bismuth salt in preference to any other form of administration of the heavy metals the important questions arise Shall these drugs be administered separately or together and shall treatment be continuous or intermittent? It has not yet been shown that the simultaneous administration of an arsenical and a heavy metal is productive of

better results, in terms of disappearance of surface organisms, healing of lesions serologic reversal or ultimate outcome, than when the drugs are given separately In addition, the combined method of use is open to one practical and one theoretical objection. From the practical standpoint, it is probably true as indicated by Loewy Wechselmann and Elcke, that the potential toxicity of arsphenamine is increased when it is given in prolonged association with mercury Mercury or bismuth the former more than the latter may produce definite renal damage. If this occurs in a patient who is taking an arsenical drug and its excretion is impaired, its toxicity both so far as the kidney and the liver are concerned may be materially intensified. The simultaneous administration of the two types of drugs over a long period of time carries a definite added risk to the patient. This added risk may be compensated for by a reduction of the average dose both of the arsenical and heavy metal which entails, however a probable sacrifice of therapeutic efficiency If the drugs are given simultaneously intermittent treatment with interpolated rest periods is necessitated. One arrives at a point at which the patient's tolerance for toxic drugs is reached and when, in order to avoid serious accident, a rest period is essential.

The theoretical objection to simultaneous treatment is the possibility of the production of drug fast strains of organisms (see page 220) The occurrence of so-called treatment-resistant cases of syphilis in human beings shows that the same phenomenon may occur in some patients. It is theoretically conceivable that, to some extent, it may occur in all patients. If it does a point may be reached where the patient's organisms are tolerant at one and the same time to arsenical and heavy metal and a rest period must be instituted in order to permit this tolerance to be lost before resuming treatment. In the test-tube and in the experimental animal drug fastness is an acquired characteristic which is specific for the drug employed, that is, a strain of organisms tolerant to arsphenamine does not thereby acquire a tolerance to bismuth and mercury and vice versa and the phenomenon of drug tolerance is lost as soon as contact with the drug is discontinued Advantage may be taken of this fact in the treatment of human beings by alternation of drugs rather than by their simultaneous use

Harrison who is an ardent advocate of combined intermittent treatment, bases his contention in part on the apparently high incidence of neurorecurrence at the Johns Hopkins Clinic, where the first course of treatment consisted of arsphenamine alone, as contrasted with its low incidence or almost complete absence from his own clinic at Saint Thomas' Hospital, where an arsphenamine and a heavy metal are used in combination. The comparison as Harrison has drawn it is not entirely just, since the incidence of neurorecurrence at the Johns Hopkins Clinic is not as high as was indicated by the inaccurate statistical method employed in our 1926 paper On the basis of the data supplied by the C C.G where the incidence of relapse of various sorts is related to the total number of pa-

In a recent careful study however Belding shows that in early syphilis, arsphenamine + bismuth reverses the serologic test more rapidly than arsphenamine alone.

tients treated the percentage incidence of *neurorecurrence is no higher* at the Johns Hopkins than at those other clinics of the Group which employ combination therapy for the first course of treatment. However, it does seem definite that the administration of a small amount of heavy metal early in the course of treatment serves as some protection against the appearance of this particular form of relapse For this reason, we believe that combined treatment with arsphenamine and a heavy metal *should* be employed *during the first few weeks* of the management of a patient with early syphilis, and that a short period of combined use does not materially enhance the risk of toxic effects Following the first course of treatment, however the two types of drugs should be used in alternation and not together

Continuous versus intermittent treatment —The study of the C C G has shown quite clearly that the *continuous* treatment of early syphilis is so far superior to any intermittent or irregular system as to leave no room for comparison. The word ' continuous implies that treatment proceeds from start to finish without interpolated rest periods of any sort. This principle of treatment is the most important element of the management of early syphilis and is now generally accepted by syphilologists everywhere

Because of its great importance, it is of interest to trace briefly the historical development of the idea. Ricord was apparently the first to advocate the continuous mercurial treatment of syphilis as long ago as 1838. Although he did not lack disciples his greatest pupil, Fournier abandoned continuous treatment and introduced the plan of chronic intermittent treatment with mercury over a period of 3–5 years. This was the system in general use up to 1910 With the introduction of the arsphenamines, it was first thought that one or at most a few injections of this drug would cure ' syphilis. The experience of observers everywhere during the first few years indicated quite clearly that this was not the case but that, instead, treatment must be prolonged and that arsphenamine must be used in some fashion in combination with a heavy metal. Most workers clinging to Fournier's idea of chronic intermittent treatment, developed plans of therapy including the combined use of arsphenamine and mercury courses of these two drugs being separated by rest periods In 1916–17 Keidel introduced in the Johns Hopkins Syphilis Clinic the idea of the continuous use of arsphenamine and a heavy metal in patients with early syphilis. His plan of treatment was based on a thorough consideration of the effects of antisyphilitic drugs and of the biology of early syphilis. We quote from a paper published in 1926 (Moore and Keidel) the reasons which led to this decision —

A few patients with primary or secondary syphilis may be cured by a single course of arsphenamine alone, or of arsphenamine plus mercury In the majority however biologic cure does not result from a single course of treatment and virulent treponemes remain in various foci in the body It is of paramount importance to consider the reaction of the patient to these undestroyed organisms. Though the nature of immunity in syphilis is imperfectly understood, the course of events in an untreated infection with gradually developing insusceptibility to reinfection and culminating

in spontaneous disappearance of the secondary outbreak, the destruction of large numbers of treponemes and latency indicates a considerable degree of resistance on the part of the patient. If treatment is begun in the primary or secondary stage of the disease, and the sequence of general tissue reaction, appearance of lesions and their spontaneous resolution is sharply interrupted, the development of the patient's own resistance against the treponeme is wholly or partially prevented. The patient thus enters on the first rest period without adequate resistance against the living treponemes remaining in his tissues and must elaborate his immune reactions afresh. Depending on the location of the surviving organisms, and the length of time between treatment courses, he may repeat the process of general dissemination and tissue reaction culminating in delayed or recurrent secondary syphilis or he may develop that bugbear of early syphilis a neurorecurrence.

"If, on the other hand, treatment is continuous, courses of arsphenamine alternating with courses of mercury the situation is theoretically quite different. When the first arsphenamine course has been completed, and the remaining organisms, if present, have perhaps acquired some degree of arsenic tolerance, it is possible to shift at once to mercury *

"After a few weeks of mercury therapy it may be safely assumed that any arsphenamine tolerance acquired by the organisms in the first course has been lost, and the powerful treponemicidal attack of arsphenamine may again be utilized. This type of continuous treatment with alternating courses of the two drugs may be continued indefinitely without detriment to the patient.

From the purely theoretical standpoint, the course of events under the intermittent and continuous plan of treatment may be shown diagrammatically as in Fig. 19 In this chart, the ordinate represents the number of treponemes in the patient's body the abscissa the element of time. Under the system of combined arsphenamine and mercury courses, separated by rest periods, the chart becomes a series of gradually descending curves, which one hopes may ultimately reach the base line. With continuous treatment with alternating courses of the two drugs, the progress of the curve toward the base line of no organisms and cure is steady and uninterrupted.

In spite of the fact that this system of continuous treatment had been in use in the Johns Hopkins Clinic from 1916–17 on, it was not described by us in the medical periodical literature until the publication of the above paper in 1926. Priority in publication of the continuous method of treatment belongs therefore to Almkvist, whose first paper on the subject appeared in 1920. Almkvist's reasons for adopting this scheme of treatment were identical with those which led Keidel to its use. Certainly credit for recognition of the great value of continuous treatment in early syphilis and for popularization of the idea to the point of its general adoption throughout the world, belongs to Keidel in this country and to Almkvist abroad.

An evaluation of various methods of treatment of early syphilis was

* Where the word "mercury" is used in the 1926 paper the words "bismuth or mercury" must now be understood.

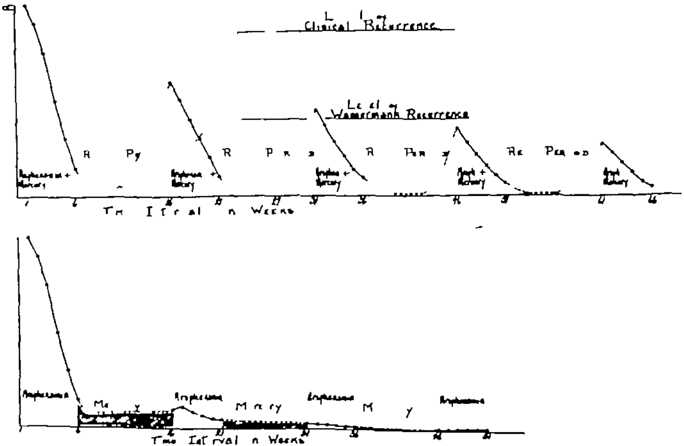


Fig. 19.—To show theory of biologic response to treatment under (a) intermittent treatment (b) continuous treatment (after Moore and Keidel)

The ordinate represents the number of treponemes in the patient's tissues the abscissa, the element of time.

made in 1935 by Martenstein, assisted by a committee of experts under the sponsorship of the League of Nations. In a review of the ultimate results of 13 198 patients from France, Germany Denmark Great Britain and the United States, the committee reported that the most successful methods for the treatment of early syphilis were

1 The continuous method of treatment as such

2. The intermittent method of treatment, as carried out in Denmark or Great Britain

The committee pointed out that since insoluble bismuth salts and arsphenamine were administered simultaneously in Great Britain and Denmark, the intermittent treatment schemes employed in these countries might in effect be continuous as a result of the continued absorption of bismuth after a temporary suspension of treatment. It insisted, however upon a scheme of treatment which would maintain a persistent attack upon the disease and avoid intervals sufficiently long to permit a remultiplication of treponemes.

The extent to which the theoretical considerations of the desirability of continuous treatment have been justified in the hard school of clinical experience is amply illustrated by the analyses of Kemp and Moore, the C.C G Millan, and especially Padget. Table 33 shows the ultimate out-

TABLE 33

THE OUTCOME IN VARIOUS TYPES OF EARLY SYPHILIS AS COMPARED WITH THE CHARACTER OF TREATMENT IN PATIENTS OBSERVED FOR 2 OR MORE YEARS

(Data of C.C.G)

Type of treatment	Total cases treated	Satisfactory clinical† results obtained, per cent
Continuous	172	79 7
Intermittent	595	65 0
Irregular	546	33 3
Intensive	47	23 4
Total	1360	53 7

"Continuous" = Uninterrupted treatment with an arsphenamine and a heavy metal, usually administered in alternation.

"Intermittent" = Treatment interrupted by short rest intervals of 1 month or more, purposeful or not.

"Irregular' = Treatment absolutely irregular, no regular system consistently or even approximately followed.

"Intensive" = An intensive arsphenamine phase (3–4 injections in 3–6 days) alternating with a more or less prolonged heavy metal course. The so-called Pollitzer system.

† Satisfactory results = All patients with reinfection all those satisfactorily completing a year of probation (no lesions of syphilis, repeated negative serologic tests, negative cerebrospinal fluid, normal physical examination) a few patients who had entered upon but not yet completed the probationary year with all findings negative.

come expressed in terms of satisfactory clinical results of 1,360 patients studied by the C C G , all *of whom were under treatment or observation* for more than 2 years. Three facts stand out clearly that continuous treatment is vastly superior to any other method, that planned treatment by the intermittent system is superior to equivalent total amounts of drug given by the haphazard irregular or intensive systems and that the results of the intensive (Pollitzer) system are about as bad as treatment

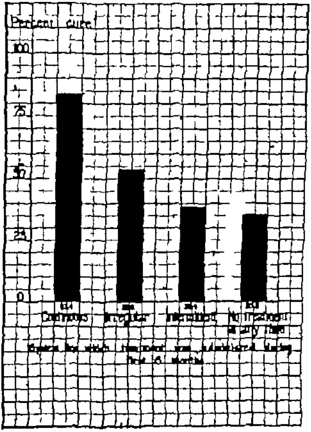


FIG. 20.—Outcome with reference to the system of treatment for the first 6 months (Padget)

given haphazardly irregularly and by no system at all, The greatest advantage of continuous therapy is apparent in early secondary syphilis, where satisfactory results were obtained by various treatment systems as follows continuous 81 per cent intermittent, 61 per cent irregular 30 per cent intensive 12 per cent

The value of continuous treatment in contrast to irregular intermittent treatment is further shown by Padget's recent re-study of the Johns Hopkins material (*Figs 20 and 21*) *Of those patients whose treatment* for the first 6 months was regular 83 4 per cent attained cure. If treat-

ment was continuous for the following 6 months cures' increased to 90 4 per cent. In contrast, only 53 0 per cent of the patients whose treat ment was intermittent or irregular during the first 6 months experienced "cure" and if treatment so continued during the following 6 months no improvement in the ultimate outcome was noted. On the other hand the institution of continuous treatment after 6 months of irregular or inter mittent treatment increased the chances of a favorable outcome from 53 8

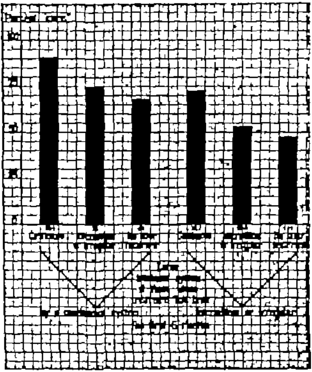


FIG. 21.—Outcome with reference to the system of treatment after the first 6 months. Note that continuation of irregular treatment did not improve the final results (Padget)

per cent to 72.7 per cent. Conversely the incidence of cure (83 4 per cent) among patients treated continuously during the first 6 months fell appreciably if the treatment for the subsequent 6 months was irregular or inter mittent (75.0 per cent cured") The absolute necessity for continuity of treatment regardless of the total amount received is shown in Fig. 22. As one would expect, patients who receive any stated amount of arsphenamine during a given period do better the shorter the interval during which it was administered. Thus patients who receive 7–9 injections of arsphen amine during the first 3 months of treatment fare as well as those who receive twice as much treatment scattered over the first 2 years.

Permanent reversal of serologic tests to negative is secured within 3

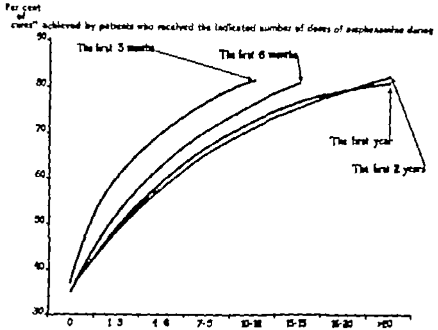


Fig. 22.—Outcome with reference to number of doses of arsphenamine received during first 2 years of treatment (Padget)

months of treatment in 52 per cent of patients with early syphilis treated continuously (Table 34) as contrasted with only 4 per cent reversals in a similar time period in patients treated intermittently and in none of those treated irregularly * Furthermore ultimate reversal is secured in 30–40

TABLE 34

RATE OF REVERSAL OF SEROLOGIC TESTS IN EARLY SYPHILIS UNDER DIFFERENT SCHEMES OF TREATMENT*
(Data of C.C.G.)

Serologic test reversed in	Percentage of patients in whom serologic tests were reversed under stated treatment scheme		
	Continuous	Intermittent	Irregular
3 months or less	52 6	3 8	—
4–12 months	29 2	33 5	4 7
13–30 months	3 4	15 8	19 0
30 or more months	1 5	4 0	24 0
Total reversals	86 7	57 1	47 7

Omitting consideration of the total amount of treatment administered.

It must be emphasized that data such as these will vary from clinic to clinic, or in the same clinic from time to time depending on the sensitivity of the particular serologic test employed

per cent more of patients treated continuously than in those managed by other systems "Intensive" treatment is not shown in this table because of the small number of patients treated, but under this system persistent serologic positivity is the rule.

Considered from the standpoint of the incidence of seroresistance for a year or longer the great superiority of continuous over other treatment schemes is also obvious (Table 35) As contrasted with late syphilis, persistent serologic positivity (fastness) is the exception in well-treated patients with early syphilis. When it does occur it may be an expression of the existence of asymptomatic neurosyphilis or much oftener of the type of treatment given. Sixty-eight per cent of patients with early syphilis treated irregularly are seroresistant, as contrasted with only 11 per cent of those treated continuously

TABLE 35

SERORESISTANCE UNDER VARIOUS TREATMENT SCHEMES IN EARLY SYPHILIS
(Data of C.C.G.)

Treatment scheme	Total patients treated	Per cent seroresistant
Continuous	1423	11.2
Intermittent	1103	37.3
Irregular	363	68.3

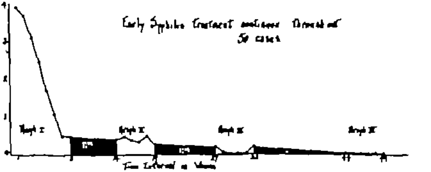


FIG. 22A.—The composite Wassermann curve of 50 patients with early secondary syphilis, treated continuously for four courses of arsphenamine plus interim mercury (Moore and Kemp)

In this and subsequent charts, the ordinate represents the degree of fixation of the Wassermann reaction the abscissa, the element of time, or the number of arsphenamine injections.

If one charts the trend of the blood Wassermann in patients treated continuously it is found to be consistently downward toward a permanently negative result (Moore and Kemp Fig. 22A) This curve may be contrasted with the trend of the blood Wassermann in patients treated

intermittently (shown in Fig. 23 for seronegative primary and in Fig. 24 for seropositive primary and early secondary syphilis) In this series of patients intermittent treatment consisted of one or more courses of arsphenamine, followed or not by a heavy metal but always with an involuntary (from our standpoint) rest period without treatment before the subsequent arsphenamine course. The Wassermann curve in the groups

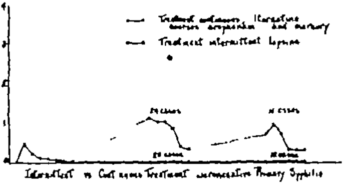


FIG. 23.—The composite Wassermann curve of seronegative primary syphilis intermittent *versus* continuous treatment (see text) (Moore and Kemp)

receiving lapsing or intermittent treatment is in striking contrast to the average curve in those treated continuously During every interval without treatment the Wassermann tends to recur toward positive. Further more the response of the test to the second and subsequent courses of

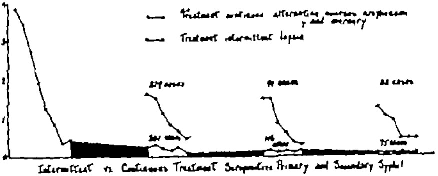


FIG. 24.—The composite Wassermann curve for combined seropositive primary and early secondary syphilis intermittent *versus* continuous treatment (Moore and Kemp)

arsphenamine is not so prompt as from the first course and tends to become less with the passage of time The rise toward positive is almost as great during each lapse from treatment These curves, based on actual experience should be compared with Fig. 19 illustrating the theory of continuous as opposed to intermittent treatment in early syphilis. The actual curves of serologic response are identical with the theoretical curve.

The influence of various arsenical drugs on the serologic test—Utilizing quantitatively titred serologic tests Moore and his associates have shown (Fig. 25) that the rate of disappearance of reagin from the blood in patients with seropositive primary or early secondary syphilis is approximately the same after treatment with arsphenamine, mapharsen, silver arsphenamine, and bismarsen, and is distinctly slower when neoarsphenamine is employed.

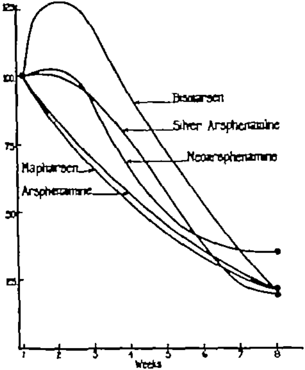


FIG. 25—The response of the quantitative titered Wassermann test in early syphilis (Moore)

The influence of collateral factors on the rate of serologic reversal in early syphilis—An important and careful study by Crosby and Campbell indicates that race sex pregnancy age of the patient, season of the year and various other minor collateral factors do not influence the rate of disappearance of reagin in the blood of persons with early syphilis under arsenical treatment but that reagin titre falls more rapidly in patients with seropositive primary than in secondary syphilis and in those with "trivial" lesions of secondary syphilis than in those with florid" lesions.

The influence of race sex and pregnancy upon the outcome of treatment in early syphilis - The influence of race and sex upon the

outcome of early syphilis is shown in Fig. 26 As one would expect, it was more satisfactory in women than in men Divided according to race, 67 8 per cent of whites were ultimately cured, in contrast to 64.7 per cent of Negroes. Analyzed according to both sex and race a satisfactory out come was achieved in the following order white women (76 1 per cent) colored women (68 5 per cent) white men (63 6 per cent) colored men (58.3 per cent) It is important in this regard and this point will be dealt

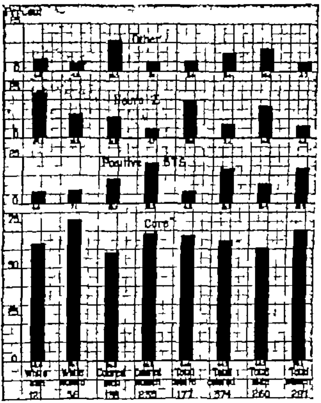


FIG. 26.—Final outcome by race and sex. Note particularly among the unfavorable results the incidence of neurosyphilis in white men and of positive STS in colored women. (Vertical columns total 100 per cent) (Padget)

with in more detail later that neurosyphilis was three times more frequent among men (16 9 per cent) than among women (6.2 per cent) and that among white patients its incidence (19.8 per cent) was approximately three times its incidence among colored (7.2 per cent) The beneficial effect of pregnancy upon the course of syphilis discussed in Chapter XXVI is further illustrated by a comparison of the final outcome of treatment in men nulliparous women and women who had experienced one or more pregnancies subsequent to acquiring syphilis (Fig. 27) A much higher percentage of the last group (74 per cent) than of either former groups

(60.8 per cent 65.6 per cent) attained cure. Whether this is due to a stimulating effect of pregnancy upon the patient's immune processes or to the possibility that because of pregnancy treatment was more intensive is not evident.

The duration of treatment in early syphilis.—Here again credit belongs to Keidel for recognition of the fact that in early syphilis, treatment, even including the use of the arsphenamines, must of necessity be

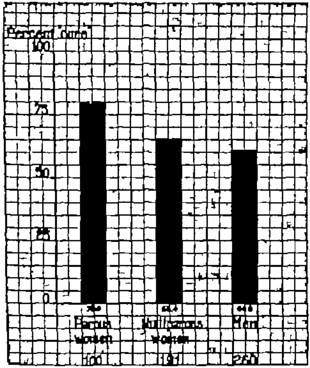


FIG. 27.—Apparent influence of sex and pregnancy on final outcome (Padget)

as prolonged as is now generally agreed to be the case. We quote again from his 1926 publication:

"When this plan was first adopted, we had no accurate idea as to how long this type of treatment should be continued. The evidence provided by patients who lapsed after varying amounts of treatment made it obvious that while a few were cured by one or two courses, many were not cured. Inasmuch as there is no way of differentiating the potential cure from the potential failure before treatment is begun, it seemed certain that the only safe procedure was to treat every patient up to the point necessary to cure the most resistant member of the group. As long as nine years ago, therefore, we set as a standard *one year's continuous treatment after the blood Wassermann (and spinal fluid) had become and had remained completely negative*."

larger amounts of treatment than this. Insistence on a minimum of 20 doses of arsphenamine in 7–8 months of treatment is as satisfactory a practical solution of the problem as can be provided.

Treatment resistance in early syphilis —The rapid disappearance of lesions (10–15 days) and of surface organisms from most lesions (6–12 hours) after an injection of arsphenamine or mapharsen is so familiar an occurrence as to attract particular attention only when it fails to happen. Rarely, about once in 500 or so patients with early syphilis, lesions fail to heal or treponemes to disappear after one or several doses. We have seen a patient, a Negro male with papulohypertrophic (condylomatous) mucous lesions on the lips which did not heal and which still contained motile treponemes during the course of 16 injections of arsphenamine. This lack of response to treatment is characteristic of early rather than of late syphilis indeed in recent literature the term arsphenamine resistance is almost entirely limited to early syphilis *

Instead of complete lack of response to arsphenamine or mapharsen there may be partial involution of lesions, with recrudescence while the patient is still under treatment with these drugs. More frequently however (in about 0 2 per cent of all patients with early syphilis) lesions heal during the arsenical phase of treatment, but relapses occur as soon as these *drugs are discontinued and a heavy metal started. These relapses may be* similar to or even in the same site as, the original lesions Or on the other hand, they may affect structures not originally involved in particular the nervous system (acute syphilitic meningitis neurorecurrence) or the eye (iritis uveitis kerato-iritis) Relapses of this sort, occurring during the actual course of bismuth or mercury therapy usually heal promptly when an arsenical is resumed but may reappear each time it is stopped and a fresh attempt made to use the heavy metal. We have seen one patient with four relapses of darkfield positive lesions on lips and tongue, each relapse appearing in the midst of a course of bismuth and healing with renewal of arsphenamine. Similar ocular relapses are discussed in Chapter XX.

There has been much speculation (Nathan, Silberstein, Moore and Robinson, Miller) as to the cause of this phenomenon. Many German observers are convinced that such cases are more frequently seen in recent years than formerly though the evidence from the Johns Hopkins Clinic *would indicate that this is not true in the Eastern part of the United* States. Treatment resistance in early syphilis is not due to any apparent decrease in the therapeutic efficacy of antisyphilitic drugs, which, under conditions of quantity production are fully as effective as, if not more so than when first manufactured in small lots. It is ascribed by some to the hypothesis that the universality of arsphenamine treatment is gradually pro-

* Certain lesions of late acquired or congenital syphilis, as for example secondarily infected bone lesions, interstitial keratitis, etc., heal very slowly under the influence of antisyphilitic drugs, but this is not regarded as arsphenamine resistance in the same sense as the analogous phenomenon in early syphilis, nor is the term "resistance" applied to the slow or absent response obtainable in certain types of visceral or neurosyphilis.

ducing a strain or strains of organisms resistant to the drug This property of acquired drug resistance of organisms has been definitely demonstrated for trypanosome infections, and is suggested for *T pallida* by the *in vitro* experiments of Akatsu and Noguchi, who claim to have gradually accustomed culture *pallida* to increasing concentrations of arsphenamine and mercury so that finally they multiplied in a concentration many times greater than that originally lethal. However they found that this resistance was rapidly lost when *T pallida* were transferred back to a drug free culture medium. Experimentally this question has been studied by Beerman, Klauder, and Greenbaum and Rule, all of whom report inconclusive or conflicting results. Beerman, in a study which includes a complete review of the entire question, thought he was able to demonstrate arsphenamine resistance in rabbits inoculated with a strain of treponemes recovered from a patient with arsphenamine resistant early syphilis. Unfortunately the experiment was not carried far enough to be conclusive and is not in agreement with similar studies of Hoffmann and Armuzzi, and Nothaas. Klauder thought he was able to demonstrate treatment resistance in animals infected with the Nichols' strain of treponemes by treating them with subcurative doses of arsphenamine. In an almost identical experiment Greenbaum and Rule came to exactly opposite conclusions. Probably the cause of arsphenamine resistance is due, not to any defect in the drugs employed or to alteration in the biologic properties of the strain of invading organisms, but to some alteration in the reaction of the patient to infection or in the manner in which his tissues metabolize antisyphilitic drugs.

In favor of the possible altered reactivity of the patient to infection is the fact that in many arsphenamine resistant patients the serologic response to infection and to subsequent treatment is quite different from that of the average individual with early syphilis. Seronegative secondary syphilis with modern serologic methods is rare (probably less than 1 in 1 000 cases) but arsphenamine resistance or a tendency to frequently repeated infectious relapse in spite of treatment was about five times as common in patients with seronegative secondary syphilis (using the serologic methods of 1917–1925) as in those who then had strongly positive serologic tests. When the serologic tests are quantitatively titered, it is found that included in the arsphenamine resistant and chronically relapsing groups are many patients with relatively small amounts of reagin in the blood. Similarly in such patients the serologic tests tend to be more readily reversed to negative by treatment than in the average patient (Moore and Kemp)

As to the possibility that such patients metabolize arsphenamine differently from other individuals, it has been pointed out by Jessner and others that patients with arsphenamine resistant syphilis often react badly to the drug, in the sense that annoying or moderately severe reactions of all types seem more frequent in them than in other patients. Jessner suggests on this basis that in such patients the therapeutic potency of arsphenamine may also be reduced. This suggestion receives added weight from the fact that resistance to arsphenamine is often specific for a single member

of the arsphenamine group i.e. lesions which fail to heal under treatment with neoarsphenamine will often heal promptly after arsphenamine or silver arsphenamine, or *vice versa*. Even though this may not be true, the phenomenon is almost always group specific, i.e. if lesions fail to heal after any of the arsphenamine products, they usually clear up promptly after the administration of bismuth or mercury, or *vice versa*. It is exceedingly rare to find a patient whose lesions are resistant to all three drugs.

The management of the treatment resistant patient—In the management of a patient with treatment resistant lesions, therefore, the first steps to be tried are (1) a change in the drugs employed (2) an intensification of treatment in the direction of larger doses and shorter intervals between doses, and (3) the simultaneous use of an arsenical drug, a heavy metal, and potassium iodide. For example, if the patient's lesions fail to heal during the first course of arsphenamine or relapse during the ensuing heavy metal course, one might profitably change to 0.3 gm. silver arsphenamine, or to neoarsphenamine 0.9 gm. given twice weekly each injection combined with a simultaneous intramuscular injection of a soluble bismuth compound, and with the daily oral administration of 8–10 grams of potassium iodide or to mapharsen 0 06 gm. every other day in conjunction with potassium iodide and a soluble bismuth compound twice weekly This intensified plan of treatment should be kept up for at least 10 injections of the new arsenical product subsequent treatment should be absolutely continuous with no rest intervals permitted, and its intensity gradually tapered off with alternation of an arsenical drug, bismuth, and mercury until continued freedom from further relapse and persistent serologic negativity for a full year has demonstrated the safety of discontinuing treatment.

Sometimes even such drastic measures will fail to heal lesions or to prevent further relapse when the arsenical drug is discontinued. Under such circumstances all drug therapy should be withheld temporarily and the patient treated with some type of fever preferably induced malaria. Immediately on its conclusion, arsenicals and heavy metals should be resumed In our experience, and in that of Dennie and McBride the response of a considerable group of such patients so treated has been most gratifying. Lesions have healed and remained healed, without further relapse, and in some instances serologic tests persistently positive during previous treatment are reversed to negative after completion of the malaria. Apparently fever therapy effects some alteration in the patient's response to his own invading organisms, or in the way he metabolizes antisyphilitic drugs or both.

It goes without saying that the treatment resistant patient must be especially warned as to the danger of transmitting his infection to others, and that sexual intercourse, kissing, and other intimate contacts should be scrupulously avoided until at least a year after all lesions have healed.

The serologic control of treatment—In our own clinic a serologic test is carried out at frequent intervals. During the arsenical courses the test is made once a week, and is often done in the midst of a course of heavy metal. This procedure, invaluable from the standpoint of study is

not necessary for the practitioner He should, however, be able to date approximately the time at which the serologic test first becomes negative or in patients with seronegative primary syphilis, to assure himself that it does not become positive. In practical terms this means that it is desirable to perform a serologic test before any treatment is given once in the middle and once at the end of the first course of arsphenamine and thereafter at the beginning and end of each arsphenamine course It seems unnecessary to add, although we know from bitter experience that the comment is still essential, that treatment must not be discontinued or even temporarily interrupted when the serologic reaction becomes negative. It cannot be too often or too strongly emphasized that the obtaining of a negative serologic reaction in early syphilis has nothing whatever to do with ultimate "cure and that to stop or to interrupt treatment at this point exposes the patient to very grave danger of subsequent and possibly disastrous relapse. *Treatment should be continued for one full year after the serologic tests have become and have remained completely negative.*

For accuracy in clinical study quantitative serologic tests are highly desirable. However for the routine management of early syphilis they are not only time consuming and expensive but unnecessary Adequate serologic control in the treatment of early syphilis is afforded by qualitative tests and we see no reason for the insistence upon routine employment of the more elaborate quantitative procedures.

Special features of the serologic response in early syphilis — In the clinical material on which these studies are based, the serologic test (Wassermann reaction) was performed by a qualitative technique. Even with this technique Kemp and Moore felt that it was sometimes possible, on the basis of the patient's serologic response during the first course of antisyphilitic treatment, to predict the probable immediate future of a syphilitic individual. A small number of their patients with frank secondary syphilis had negative serologic reactions (1–1½ per cent) About 10–15 per cent of patients with seropositive primary or early secondary syphilis showed very rapid serologic reversal after the initiation of treatment—that is a positive serologic test became negative after one or two injections of arsphenamine, whereas in the average patient this result was not achieved until the sixth or eighth week of treatment. In these two groups of cases, seronegative secondary syphilis and those with "prematurely negative serologic tests under treatment, early infectious relapse was about five times greater than in the average patient with early syphilis. This suggests that these types of serologic response indicate an inability of the patient to react to the presence of the treponeme by the usual defensive processes, and that a lapse in treatment is likely to be followed by a redissemination of organisms and possibly the involvement of important structures, such as the nervous system which may have escaped the first generalization In such cases it is even more essential than usual that treatment be intensive and continuous, so that treponemicidal drugs may accomplish the destruction of the organisms which the patient is unable to deal with himself

Seroresistance in early syphilis —At least two factors operate to

produce the condition of seroresistance (i.e. serologic tests persistently positive for 6 months or longer) in early syphilis. One of these, the influence of intermittent, irregular or "intensive" (Pollitzer) treatment, has already been considered (Table 35) The other is the influence of invasion of the central nervous system. This may be clearly seen from Table 36, based on a correlation of blood and spinal fluid examinations in 2,117 patients of the C C G Not only is the incidence of seroresistance higher in patients with abnormal than in those with normal spinal fluids but

TABLE 36

THE RELATIONSHIP OF SERORESISTANCE AND SPINAL FLUID ABNORMALITIES IN EARLY SYPHILIS
(Data of C.C.G)

Cerebrospinal fluid	Total patients	Per cent seroresistant for 6 months or longer
Normal	1522	16 0
Group Ia Cells 6 or over all other findings negative	146	15 8
Group Ib Cells 5 or over excess protein WaR and colloidal test negative	195	22 6
Group II Cells and protein + or − WaR partial positive, colloidal test + or −	228	45 6
Group III Paretic formula	26	42 3

also the more abnormalities present in the fluid the higher the percentage of persistently positive tests in the blood In any patient with early syphilis, therefore, and particularly in those treated continuously the persistence of positive serologic tests for syphilis for 6 months or longer is a good index of probable neuraxis involvement, and demands immediate study of the cerebrospinal fluid if this has not already been done.

In patients with early syphilis treated continuously and with normal spinal fluids, seroresistance is a very infrequent phenomenon, occurring *in not more than 2–5 per cent of such individuals in contrast to its 30–50* per cent incidence in most types of late syphilis. Its significance in early syphilis when the cerebrospinal fluid is normal is not yet clear nor is its relationship to an ultimately favorable or unfavorable clinical outcome We have the impression, however that it is definitely of graver prognostic import in early than in late syphilis and that every effort should be made, by means of continuous and prolonged treatment, to reduce the test to *negative* and to *maintain* it so This is the *reverse* of our position as to seroresistance in certain types of late syphilis where a persistently positive test over long periods of time apparently does no harm

The significance of serologic relapse in early syphilis.—The term serologic relapse implies that the serologic tests negative at the

start of treatment, as in seronegative primary, or reversed to negative by treatment, as in seropositive primary or early secondary syphilis subsequently become positive. This may occur actually during the early part of treatment as an apparent provocative phenomenon * or later after serologic reversal, if the quantity of reagin of the blood has been reduced to a low level, but not yet completely eliminated. (With the routine Wassermann technique, a negative test may be obtained while as much as 6 units of reagin persist in the blood.) This form of serorelapse is of no particular significance, except to serve as a landmark for the duration of treatment which should continue for one year after complete serologic reversal.

A second and more common form of serologic relapse is that which occurs after an interval without treatment. Under these circumstances, it appears with about equal frequency in association with a simultaneous clinical relapse or as an isolated phenomenon, and in direct proportion to the *amount of treatment administered before the rest interval (purposeful* or otherwise) When this form of serologic relapse occurs within the first 4 years after the infection (as it usually does) and regardless of the amount of treatment the patient has already had, it must be regarded we believe, *as evidence pointing for all practical purposes to a general redissemination* of the virus, rather than due to any local lesion. If this concept is correct, its significance for the patient and the community is identical with that of a fresh syphilitic infection. Treatment must be promptly recommenced as for early secondary syphilis and carried through to the same conclusion, i.e., *after the relapse* continuous treatment for one year after serologic tests of blood and cerebrospinal fluid have become and have remained negative.

A phenomenon very difficult of interpretation is the weakly positive serologic test interspersed in the midst of a long series of negative tests in a patient who has completed treatment and is undergoing probationary observation. The physician even the expert, is often at a loss to decide whether this is because of slight variations in laboratory technique or whether it has any significance for the patient s future. The nearest approach to a solution of this problem is offered by the material of the C.C G Here the *ultimate clinical* outcome was determined in 118 patients in whom this type of serologic response occurred. Definite clinical relapse of one or another form followed the incompletely positive serologic test at varying intervals in 11 per cent, and definite serologic relapse in an additional 6 per cent. *On the other hand* 32 per cent of such patients went on to an ultimately satisfactory outcome with subsequent freedom from clinical lesions and with subsequently persistently negative serologic tests. On the basis of this information it appears that such patients should be *even more carefully followed than the average individual with treated* early syphilis, but that the development of such a weakly positive test is not necessarily an indication for the immediate resumption of antisyphilitic therapy

* There is grave doubt concerning the occurrence of a genuine provocative phenomenon in either early or late syphilis (see Chapter XXVIII)

have repeated recurrences of one or another type. This is particularly true of those whose initial relapse is early infectious (mucocutaneous or ocular especially the latter) or late benign in type. Further relapses may occur after seemingly adequate treatment and patients who have shown a *tendency to relapse should* be kept under particularly strict post-treatment observation

Probation and subsequent post treatment observation—The point at which *treatment may be safely discontinued depends on the* character and duration of treatment, and on the presence or absence of serologic or clinical relapse

(a) If treatment has been continuous throughout, it *may be stopped* after a full year of serologic negativity

(b) If the patient has been uncooperative and has interpolated intervals without treatment of more than a month so that treatment has been intermittent or irregular the requirement of a year of serologic negativity is not sufficient. Under these circumstances treatment should be continued even though the serologic tests are persistently negative, until five full courses each of an arsenical drug and a heavy metal have been given, no matter whether this involves 2, 3 or 5 years of treatment.

(c) In the remote event of persistent unexplained serologic positivity a minimum of 2 full years of treatment—the approximate equivalent of 8 full courses each of an arsphenamine and a heavy metal—should be insisted upon.

When treatment is stopped, the patient must understand that determination of the probability of ' cure depends largely on his clinical and serologic behavior during the first year thereafter To qualify for cure *he must, within this period of time*—

1 Take no treatment of any kind.

2. Develop no lesions of syphilis.

3 Maintain a persistently negative blood serologic test, which should be repeated monthly if possible, or at least as often as every two months.

4. At the end of the year complete physical examination, with special reference to cardiovascular and central nervous systems, must show no abnormalities attributable to syphilis and these negative physical findings should be checked by a repeat negative test of the cerebrospinal fluid and by normal teleroentgenographic and fluoroscopic findings as to *aortic width and elasticity (see Chapter XVIII)*

If these requirements are fulfilled the patient may be regarded as probably cured and if he desires, may be allowed to marry In order to guard against the approximate one chance in twenty of subsequent progression or relapse however further observation is desirable. This should consist during the second year of serologic tests every 3 months during the third year every 6 months and thereafter yearly *for the duration of* life The cerebrospinal fluid need not be retested if the first examination during treatment, and the second at the end of the year of probation, have *both been negative. Complete physical re-examination* should be carried out at least as often as every two years, preferably by the same physician so that the significance of minor changes, if any may be correctly inter

preted. Complete normality for 5 years after the cessation of treatment probably implies permanent cure (Padget) All this may appear, to patient and physician alike, as unnecessary caution. We can testify from long experience, however that it is distinctly worth while as a method of early detection of such crippling and dangerous late lesions as aortitis and that the relatively small inconvenience and expense to the patient is more than compensated for by his added security and peace of mind. Periodic re-examination is the best form of life insurance for the treated syphilitic.

If at any time during post-treatment observation a clinical or serologic relapse appears, treatment should be promptly reinstituted as indicated in preceding paragraphs

TABLE 38

THE PRINCIPLES OF TREATMENT OF EARLY SYPHILIS

1. The aim of treatment is radical cure.
2. Study the patient before treatment to determine
   a. Complications of syphilis
   b. Other complicating diseases
   c. Base-line physical findings, to compare with subsequent examinations.
3. Examine contacts.
4. To secure maximum treponemicidal effect, use
   a. Old arsphenamine (606) or mapharsen in place of other arsenicals.
   b. Bismuth in place of mercury
   c. Concentrate on maximum arsenical dosage and regularity during the first 3 months of treatment.
5. Treatment must be continuous—no rest periods.
6. Use the arsenicals and heavy metals in alternating courses—not in combination.
7. Utilize serologic control, including cerebrospinal fluid, to determine duration of treatment.
8. Prolong continuous treatment for one full year after blood and cerebrospinal fluid tests become and remain permanently negative.
9. Follow treatment with rigidly controlled year of probation.
10. Thereafter follow patient for his lifetime (or for an absolute minimum of 5 years) with periodic physical and serologic examinations.

Summary of the principles of treatment of early syphilis.—The various principles of treatment which have been discussed in detail may be very briefly summarized as in Table 38. Their validity is established by the evidence which has been presented, and their universal observance would do much toward eliminating syphilis as a major [illegible] and toward preventing the disastrous late developments of the disease.

Suggested outlines of treatment for early syphilis.—In [illegible] Moore prepared for the United States Public Health Service with the collaboration and essential agreement of other syphilologists (Cole, Schamberg, Solomon Wile and Stokes) a brief outline of treatment for early syphilis With certain minor modifications, suggested by further experience this outline is reproduced herewith (Table 39). The practitioner would do well to follow it in the uncomplicated case of early syphilis as

TABLE 39

A SCHEME OF TREATMENT FOR EARLY SYPHILIS (ARSPHENAMINES)

Day or week	Arsphenamine	Interim treatment	Serologic reaction	Remarks
Day				
1	0.3–0.6	Bismuth 0.2 gm simultaneously with first 4 doses of arsphenamine.	1	Arsphenamine dosage for first 3 injections at level of 0.1 gm. for each 25 pounds body weight. Average subsequent dosage, 0.4 gm. men 0.3 gm. women. In average patient all lesions heal rapidly and serologic reaction becomes negative during first course. If arsphenamine cannot be used, substitute 8 to 10 doses 0.3 gm. silver arsphenamine, or 10 to 12 maximum doses 0.9 gm. neoarsphenamine. This applies also to subsequent courses.
5	0.3–0.6			
10	0.3–0.6			
Week				
3	0.4			
4	0.4			
5	0.4			
6	0.4			
7	0.4			
8		Bismuth, 4 doses 0.2 gm., and K I or Ung Hg and K I	1	If mercury is used, note overlap of 1 week at end of first and start of second arsphenamine courses. No overlaps necessary with bismuth. At this point a few days without treatment may be dangerous. Neurorecurrence.
9				
10				
11				
12	0.4		1	Arsphenamine starts, bismuth stops. Watch for provocative serologic reaction after first dose of arsphenamine.
13	0.4		1	
14	0.4			Try to prevent short lapses in treatment, especially at this early stage.
15	0.4			
16	0.4			
17	0.4		1	
18–23		Bismuth, 6 doses, or Ung Hg and K I		Bismuth is better than mercury. Use it if possible. Examine cerebrospinal fluid routinely at about this time.
24	0.4			
25	0.4			
26	0.4			
27	0.4			
28	0.4			
29	0.4			

TABLE 39 (*Continued*)
A SCHEME OF TREATMENT FOR EARLY SYPHILIS (ARSPHENAMINES)

Week	Arsphenamine	Interim treatment	Serologic reaction	Remarks
30–37		Bismuth, 8 doses, or Ung Hg and K.I	1	Mercury inunctions may be substituted for bismuth if patient's finances or occupation (travelling salesmen, etc.) demand it.
38	0.4			
39	0.4			
40	0.4			
41	0.4			
42	0.4		1	Patients with seronegative primary syphilis may cease treatment here, if serologic reaction has always been negative.
43	0.4			Note that bismuth or mercury courses are gradually getting longer—4, 6, 8, and now 10 weeks.
44–53		Bismuth, 10 doses, or Ung. Hg and K.I	1	
54	0.4			The average seropositive primary or early secondary patient should have at least 5 courses of arsphenamine.
55	0.4			
56	0.4			
57	0.4			
58	0.4			
59	0.4		1	
60–69		Bismuth, 10 doses, or Ung Hg and K.I		It is safer to finish treatment with bismuth or mercury rather than with arsphenamine.
70–122	[1]	No treatment	6–12	Serologic test every month if possible; at least every other month.
123	Complete physical and neurologic examination, spinal puncture, and, if possible, fluoroscopic examination of cardiovascular stripe. Thereafter yearly physical examinations, serologic tests every 6 to 12 months. If the two spinal fluid examinations above are negative, this need not be repeated.			

[1] Probation

closely as possible departing from it only when complications make changes obligatory We have attempted in this chapter and in Chapter XIV following to offer further suggestions for the management of those patients in whom complications exist or arise during treatment.

In Table 40 we suggest a treatment scheme for early syphilis utilizing mapharsen in place of arsphenamine in which the arsenical injection is given twice rather than once weekly and the total number of

TABLE 40

A SCHEME FOR THE TREATMENT OF EARLY SYPHILIS UTILIZING MAPHARSEN

Days	Mapharsen	Bismuth subsalicylate
1	0 06 gm.	
3	0 06 gm.	
5	0 06 gm.	
8	0 06 gm. 20 doses	
Weeks thereafter		
2- 9 inclusive	0 06 gm. twice weekly	6th-9th week inclusive Bi 0 2 gm. weekly
10-13 inclusive		4 weekly injections Bi 0 2 gm.
14-23 inclusive	0 06 gm. twice weekly 20 doses	
24-29 inclusive		6 weekly injections Bi 0.2 gm. (Examine spinal fluid)
30-39 inclusive	0 06 gm twice weekly 20 doses	
40-47 inclusive		8 weekly injections Bi 0.2 gm.
48-57 inclusive	0 06 gm weekly 10 doses	
58-67 inclusive		10 weekly injections Bi 0 2 gm
Probation		

arsenical injections increased from 32 to 70 This we believe desirable because of the rapid excretion of mapharsen and feasible because of its low reactivity Insistence of biweekly treatment does, however introduce obvious and important practical difficulties for the patient, both as to expense and loss of time.

Fever treatment of early syphilis —The value of fever in the treatment of arsphenamine resistant syphilis has been discussed on page 222. Used as a sole method of treatment for the average patient with early syphilis all observers agree that fever therapy alone by whatever method given is worthless. Its value as an adjunct to routine treatment is yet to be determined In 1924 Kyrle published extravagant and as shown by the later work of Kerl premature claims for the combined use of neoarsphenamine and malaria. In this country Simpson and Kendell, Neymann Lawless and Osborne and Epstein and Cohen have studied the effect of combined chemotherapy and mechanically induced fever These

observers again confirmed Kyrle's observation that fever alone in the treatment of early syphilis is worthless. They also agreed with Kyrle that the combination of fever and chemotherapy offers a distinct advantage over the use of chemotherapy alone. However the number of cases treated so far is too small and the duration of follow-up after treatment too short to permit its accurate evaluation. We feel that the combination of fever and chemotherapy offers no particular advantage in the routine management of early syphilis and that the use of fever should be confined to those patients who are chemotherapeutically resistant. Even if the combination of fever and chemotherapy should prove a distinct advantage over the routine measures in use at the present time, there are distinct limitations to its application since it means hospitalization with the loss of the patient's time from work and a consequent marked increase in the immediate cost of treatment.

The further spontaneous evolution of treated early syphilis — In the discussion of Chapter III on the prognosis of syphilis and in Chapter XVI dealing with the treatment of latent syphilis, we have indicated that if early syphilis is untreated there is a tendency toward the natural and spontaneous cure of the infection. This is true whether no treatment is ever given to the patient, as in Bruusgaard's material, or whether treatment is administered late, after the appearance of secondary lesions their spontaneous healing and the development of latency. It is apparently not true, however of treated early syphilis. Table 41 indicates that the end

TABLE 41

INDICATING THAT IN TREATED EARLY SYPHILIS, THE RESULT OBSERVED WITHIN THE FIRST FIVE YEARS IS LIKELY TO BE PERMANENT AND IS NOT IMPROVED BY MERE PASSAGE OF TIME

(Data of C.C.G.)

Duration of observation	Total patients	Percentage with satisfactory outcome
2–5 years	977	53 7
5–10 years	295	53 6
10–15 years	88	80 0

result in terms of satisfactory outcome is not materially improved by the passage of time. This is a matter of considerable practical importance to the patient. He wants to know at the end of a year or two of post-treatment observation what the chances are that the result obtained at that time will be permanent. On the basis of our present information he may be told we think with reasonable assurance that if he is clinically and serologically well within the first five years of post-treatment observation he is likely to remain so for the rest of his life. He cannot be told however as can a patient with latent syphilis, that the result observed within the first few years is likely to be improved upon by his own natural resistance against the disease during the passage of further years. This

contrast between the subsequent course of early and late syphilis is certainly due to the fact that in the patient whose treatment is started early the development of his natural immune reactions is prevented by treatment whereas, in the patient whose *treatment is started late*, treatment does not interfere with the subsequent working of a defense mechanism which has already been established within the first two or three years of an untreated infection.

The striking difference between early and late syphilis in the influence of time on the ultimate outcome does not constitute an argument for deferring treatment in early syphilis until the stage of latency has been spontaneously achieved. The danger of the *spread of infection to others*, plus the superior results obtainable by treatment in early syphilis in terms of radical cure' are insistent reasons for the immediate treatment of all recently infected individuals.

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CHAPTER XIV

THE MANAGEMENT OF EARLY SYPHILIS COMPLICATED BY TREATMENT REACTIONS, PREGNANCY YOUTH OR OLD AGE, VISCERAL LESIONS OF SYPHILIS OR OTHER DISEASES

THE outline of treatment for early syphilis supplied in the preceding chapters is intended for use in patients whose age and satisfactory general physical condition justify intensive efforts at radical cure and in whom complications do not occur during treatment. Fortunately the majority of recently infected individuals fall within this category. Exceptional circumstances sometimes arise, however which necessitate modification of the plan of attack. The most frequently encountered of these complicated situations will be briefly described, and concrete suggestions offered as to how they may be managed.

The treatment of early syphilis in infants and young children. —We have seen a number of examples of extragenital chancres in infants usually on the lips from contact with lesions on the nipples of nursing mothers. Even more frequently older children (especially Negroes) aged 5 to 14 acquire syphilis either through genital or extragenital infection (Smith reports from our clinic and reviews the literature). The aim of treatment in such youthful patients is exactly the same as in adults—radical cure —and the urgency of the effort is the greater in view of the patient's youth. The fact that the expected life span is longer than in adults offers more opportunity for the development of disastrous late lesions in inadequately treated children. In infants with acquired syphilis the danger of immediate death is much less than in congenital infections, but the risk of subsequent development of cardiovascular or central nervous system syphilis is much greater.

The principles of the treatment of early acquired syphilis in children are also exactly the same as in adults i.e. maximum treponemicidal attack, continuous treatment without rest intervals and prolonged treatment based on identical serologic control of blood and cerebrospinal fluid. The choice of arsenical drugs* depends on the ease of their administration. In infants and young children, sulpharsphenamine is the drug of choice since it may be given by the intramuscular route.† Fortunately it is better tolerated by children than by adults, and such common adult complications as encephalitis dermatitis nephritis, and blood dyscrasias need not be especially feared. In older children with available veins, to whom intravenous treatment may be given without too great physical struggle neoarsphenamine or mapharsen may be used in place of arsphenamine since they are easier to give (small needle, small bulk of fluid fewer mild reactions) and since the cooperation of the child and its parents should be

* The use of acetarsone in children is discussed in Chapter XXVII

† Sulpharsphenamine should never be given intravenously

maintained so far as possible by minimizing the pain and discomfort of treatment. The arsenical preparation selected should be used as in adult patients, at the start of treatment. There is no need for preparatory heavy metal courses.

Children tolerate arsenical drugs in general in higher dosage and with fewer mild or grave reactions than do adults. Full advantage may be taken of this fact. The dosage of either sulpharsphenamine or of neoarsphenamine may begin at a level of 15 mgm per kilo of body weight, increasing promptly to 25 mg/kg., and of mapharsen 1 mg/kg. Each course of an arsphenamine may consist of 8 injections courses of mapharsen should be prolonged to 12–20 injections.

Bismuth subsalicylate may be used as interim treatment, just as in adults. The average dosage is measured on the basis of body weight (2–4 mg/kg) Or if the child's parents can be trusted to cooperate, mercury by inunction may be substituted with advantage, since this involves no pain to the child. For an infant, a daily 1 gram rub of 50 per cent U.S.P mercury ointment may be given, with proportionately larger dosage (up to 4 grams) for older children. Routine examination of the cerebrospinal fluid should be carried out as in adults.

The utmost effort must be made to secure the cooperation of parents in providing for continuous treatment, without rest periods. If the parents are recalcitrant to reason and advice, as is sometimes the case, advantage should be taken of the powers of the local Juvenile Court, which in most states has the authority to insist on the treatment of an infectious disease.

Especial caution must be taken against the infection of other children by means of the transfer of objects from mouth to mouth. We have seen at least two extragenital infections in children acquired through this habit.

The treatment of early syphilis in elderly patients —When an individual over the age of 60 acquires a fresh syphilitic infection, the problem from the public health standpoint is identical with that in younger patients but from the standpoint of the patient himself the situation is much less serious. His normal life expectancy is sufficiently short that in all probability there will not be time enough for syphilis to cause crippling damage The intensity of treatment may be relaxed, though the principle of continuous therapy to avoid neurorecurrence and infectious relapse should be maintained. Neoarsphenamine or mapharsen may be substituted for arsphenamine and the dosage level lowered to an average of 0.3–0.6 gm. or 0.03–0.04 gm. respectively depending on the general physical status. Courses of heavy metal may be longer than in younger patients, but must be given cautiously if there is any reduction of kidney function. The total duration of treatment need not exceed a year regardless of serologic progress. Routine spinal fluid examination may be dispensed with. Contrary to the frequently expressed opinion, we have no reason to believe that syphilis *per se* is more severe in elderly than in younger individuals.

The management of early syphilis complicated by pregnancy —Pregnancy is not a contra-indication to the energetic treatment of early

syphilis. On the contrary the necessity for maximum treponemicidal attack is the greater in view of the urgency of protecting the fetus. If the infection is discovered early in pregnancy before the third to fifth month, courses of an arsenical preparation alternating with courses of bismuth, just as in nonpregnant women or in men, should be employed If the patient is infected within the last 3 months of pregnancy, arsphenamine (606) should be given every week until delivery even if a series of 12–15 injections is required. In any event, the four weeks immediately prior to delivery should be occupied by *arsphenamine rather than by heavy metal* therapy If, as sometimes happens lesions are discovered for the first time on the very eve of delivery one or more injections of arsphenamine should be given, in order to destroy surface treponemes and to minimize the possibility of infection of the fetus during passage through the birth canal, or of the obstetrician himself (see Chapter XXVI)

The management of early syphilis complicated by treatment reactions —The general question of treatment following arsenical reactions has been discussed in detail in Chapter VII Here it is possible to discuss these questions only in so far as the existence of early syphilis raises special points.

Post arsenical jaundice This complication, unless it has attained the gravity of acute yellow atrophy must not prevent the further treatment of early syphilis. If jaundice appears during the midst of treatment, it is first and immediately necessary to study the patient in sufficient detail to assure oneself that it is actually or probably due to the arsenical preparation employed. Should this be the most likely explanation the drug is at once discontinued. During the acute phase of the illness which usually lasts not more than 10 days to 2 weeks, all treatment may be omitted A longer rest period than this raises serious possibilities of infectious mucocutaneous or ocular relapse, or of neurorecurrence. As soon as fever if present, disappears, and the patient feels well and even though jaundice still persists heavy metal treatment, preferably with bismuth, should be started at once and continued for at least 2–3 months. The administration of bismuth will not impede prompt recovery from the reaction. If jaundice has appeared early in the course of treatment, i.e., before at least 3 courses of an arsenical preparation have been given, it is highly desirable to resume the use of an arsenical drug after this bismuth course. This resumption may be almost always successfully accomplished

Renewed attempts to give an arsenical should not be undertaken in any case for at least 2 months after the jaundice has cleared The drug should be started very cautiously e.g with a dose of 0 05 gm of arsphenamine or neoarsphenamine or 0 01 gm. of mapharsen increasing by similar small weekly increments if no further evidence of liver damage appears, until an average therapeutic dose is reached *Careful watch should be maintained* over sclerae (for jaundice) urine (for the appearance of bile or bile pigments) and, if possible, over the urobilin content of the blood (see pp 122–123) during these therapeutic efforts.

If the original attack has been accompanied by signs of toxicity suggesting acute yellow atrophy (from which, however recovery *is unusual*), or

If in a milder case further attempts at arsenical therapy are followed by a second attack of jaundice, the arsenical preparations must be permanently abandoned. If tryparsamide is indicated because of asymtomatic neurosyphilis, it can generally be given with safety However in the absence of central nervous system involvement, reliance must be placed on the heavy metals.

Post arsenical dermatitis —The planning, and to some extent the carrying out, of subsequent treatment for a patient who has had an attack of arsenical dermatitis is the proper function of the expert, not of the practitioner The consequences of mismanagement may be disastrous. It is unfortunate that dermatitis tends to occur early in treatment, a fact of great importance in early syphilis. At one blow, the physician may find himself deprived of his chief mainstay of treatment.

What to do depends almost entirely on the type of dermatitis No further arsenicals can be administered to patients in whom the reaction is definitely on a sensitisation basis. Any product (even bismarsen or mapharsen), after any interval of time, or in any dosage, no matter how minute may cause a repetition of the reaction. Such a patient must be warned of his own sensitization, instructed to tell possible subsequent physicians of it, and advised to refuse to submit to injections of any arsenical product. The only arsenical which may be given is tryparsamide, since sensitisation is generally group specific for the trivalent arsphenamines and does not include this pentavalent drug which may be safely administered. However there is no indication for its use unless the patient has neurosyphilis. If he is free from this complication (of which one must assure oneself by routine lumbar puncture as promptly as possible after the dermatitis, if it has not already been done) further treatment must proceed with heavy metals alone. However even in the presence of neurosyphilis the patient must receive heavy metals in amounts adequate to prevent infectious relapse and progress of the disease in vital organs other than the central nervous system.

If the physician is in any doubt as to the character of a post-arsenical eruption, he should ask for expert syphilologic or dermatologic consultation while the rash is actually present. Failing such expert advice, the best that one can offer to the physician unskilled in the niceties of dermatologic diagnosis is to discontinue arsenical treatment *at once* in the event of the appearance of any apparently toxic eruption (i.e. any dermatosis not so readily familiar as acne vulgaris) occurring in the midst of arsenical therapy and to avoid further arsenical treatment until the character of the rash is clear However in recently infected patients, intramuscular bismuth for 10–12 injections should be started at once without a rest period, and even while the rash is present. No harm will be done by bismuth and continuous treatment is essential to guard against relapse.

At the end of the bismuth course, if there is still doubt as to whether the dermatitis was due to sensitization, *cautious trial of a different arsenical product* from that which caused the original rash may be attempted. Some of the milder eruptions are drug rather than group specific, e.g. produced by arsphenamine they will not be repeated after neo- or silver arsphen-

amine or mapharsen etc. (cf page 107) Initial dosage should be minute with weekly increases by equally small increments until average therapeutic dosage is reached. The patient must be questioned each week as to the occurrence of generalized itching, and his skin inspected. *If itching with or without a new rash occurs further efforts must be abandoned.* In many instances however this procedure will be successful and the patient can be treated normally without further trouble. Since in the trial course it requires 6–8 successively larger injections of the drug to arrive at an average therapeutic dose, this particular arsenical course should be prolonged to a total of 10–12 injections.

The success of this type of renewed therapy in some patients does not imply desensitization which with our present methods we believe cannot be accomplished but only that the patient in question had not been actually sensitized.

There has been some discussion, especially in the German literature as to the favorable effect of a severe attack of post-arsenical dermatitis on the subsequent course of syphilitic infection (so-called esophylaxis) This hypothesis has been generally discarded in this country We do not believe that the treatment complication has any favorable effect on the infection but, on the contrary may seriously jeopardize a patient s outcome since it may force the complete abandonment of the more efficient therapeutic measures.

Blood dyscrasias —The occurrence of a blood dyscrasia (purpura, aplastic anemia, agranulocytosis) is, provided the patient recovers a warning against any further attempts at therapy with any of the arsphenamines, although mapharsen may be given with safety in some instances (page 117) The reaction is so grave, and the danger of its repetition from renewed treatment efforts so great, that the risk cannot be accepted. Further treatment in such patients (fortunately rare) must at present be limited to the heavy metals.

Hemorrhagic encephalitis —Though we have had no personal experience with this reaction, we should lack the temerity to attempt further arsenical therapy after its occurrence, limiting our efforts to the heavy metals.

The unsupported heavy metal therapy of early syphilis —The four complications of arsenical therapy just discussed are the only circumstances which occur to us in which the arsenical preparations are absolutely contra-indicated in early syphilis In these events one must abandon hope of radical cure of the infection, unless enough of the arsenicals have been given before the accident to render "cure probable and treatment must be carried on with the heavy metals alone. Whether unsupported heavy metal therapy should be continuous or intermittent depends on the choice of drugs and the route of their administration. Our personal preference is for continuous treatment, with courses of intramuscular injections of an insoluble bismuth salt separated by courses of mercury by inunction. As we have already pointed out, the use of an insoluble bismuth salt provides to some extent for continuous therapy in any event since absorption continues for long periods of time after the

injections cease. But something is gained, we think, by filling in these intervals with mercury whose action is perhaps identical, but perhaps slightly different. At any rate it is worth trial for the sake of minimizing relapse.

How long unsupported heavy metal therapy should be continued in early syphilis depends on how much treatment had been given before the reaction occurred If less than 6 injections of an arsenical preparation the patient should be managed as in the pre-arsphenamine era i.e. 3–5 years of continuous use of bismuth mercury and potassium iodide. If more than 6 injections of an arsenical preparation have been administered before the reaction the length of heavy metal therapy may be shortened *somewhat as suggested* in Table 42 and depending largely of course, on

TABLE 42

SUGGESTED OUTLINE OF TREATMENT FOR EARLY SYPHILIS IF SOLE RELIANCE MUST BE PLACED ON THE HEAVY METALS

Amount of arsenicals given before the reaction	Duration of continuous treatment with alternating courses of bismuth and mercury	
1–6 doses	3–5 years	Remember that tryparsamide may be added to this scheme if the patient has clinical evidence of neurosyphilis or an abnormal spinal fluid.
7–12 doses	2–3 years	
13–18 doses	1½–2½ years	
19–24 doses	9 18 months	
More than 24 doses	6–9 months	

the occurrence or non-occurrence of relapse and on serologic progress. An effort should be made to prolong treatment to the point generally advised for early syphilis—until serologic tests (and cerebrospinal fluid) have become and have remained negative for one year Especial attention should be paid to examination of the spinal fluid which should be tested at about the sixth month and if arsphenamine cannot be used, retested at the end of the second and fifth years Asymptomatic neurorelapse is more likely under straight heavy metal therapy than when the arsphenamines can be used.

The management of early syphilis with associated visceral lesions of syphilis —In a relatively small number of patients with early syphilis there may be lesions of liver or kidney sufficiently extensive to produce symptoms. These lesions call for great caution in therapy

Early syphilitic hepatitis —Acute yellow atrophy associated with early syphilis is so rare that we have never seen a case. Reported instances have been so rapidly progressive and the prognosis so grave that therapeutic efforts cannot be limited to the slowly acting heavy metals. Neoarsphenamine or mapharsen should be employed. The initial dosage should be small (neoarsphenamine 0 1 gm. mapharsen 0 01 gm.) repeated every second or third day and increasing by increments of 0.1

gm of neoarsphenamine or 0 01 gm. of mapharsen at each dose. On the days on which neoarsphenamine or mapharsen are not given, mercury succinimide (0 01–0 02 gm), colloidal mercury sulphide (0 065–0 13 gm) or another soluble mercurial salt should be given intravenously This form of treatment may be continued until the outcome—recovery or death—is certain If recovery occurs subsequent treatment should be carried on very cautiously until convalescence is complete, and the patient s tolerance for arsenical drugs assured.

Jaundice without toxic constitutional symptoms occurs in about 0 1–0.2 per cent of patients with early syphilis. Its presence calls for some caution in starting treatment for example with small doses of arsphenamine (0 1 gm) but disappearance of jaundice is usually rapid recovery complete, and the dosage may be promptly raised to an average level. Subsequent treatment may be carried out as in the uncomplicated case.

Nephritis —Two forms of early syphilitic nephritis occur one more commonly than the other Many patients with early syphilis show a small amount of albumin and an occasional cast in the urine in a few these findings are associated with slight hematuria, an elevation in blood pressure, and evidences of moderately impaired renal function (low phthalein output, slight nitrogen retention) without edema. This type of renal involvement may be clinically indistinguishable from an acute glomerular nephritis due to other causes. More rarely the picture more closely resembles the classical description of syphilitic lipoid nephrosis—enormous proteinuria and cylindruria with double refractile lipoid casts, low plasma protein inversion of the blood albumin-globulin ratio edema, low blood pressure, and normal or only slightly disturbed evidence of renal function.

In either case, extreme caution in starting treatment is essential. The patient should be in bed in the hospital. An arsenical should be used rather than a heavy metal, so as not to add to the load of the already damaged kidney The initial dosage should be small (0 1 gm. arsphenamine, 0 15 gm neoarsphenamine, 0 02 gm mapharsen) but the interval between injections may be shortened to 2–3 days. If the initial dose is large, a severe Herxheimer reaction may result with anuria, increasing edema and nitrogen retention, and even uremia. The urine, blood pressure, and renal function should be carefully watched. In patients with edema, fluid intake should be limited to 1200–1500 cc daily Dietary restrictions are unnecessary unless the non-syphilitic character of the nephritis becomes clear A chart illustrative of the outcome of this method of treatment in a patient with the second type of renal involvement (nephrosis) is shown as Fig. 29 The prognosis of either type of syphilitic nephritis is good in fact, if prompt improvement does not occur one may be reasonably certain that the renal lesions are not due to syphilis In this latter event, antisyphilitic treatment should be limited to small doses (not exceeding 0.3 gm.) of neoarsphenamine or mapharsen (0 02 gm.) while other possible causes for the nephritis are searched for and until the outcome is more certain. It is necessary to control the associated infectious lesions of early syphilis and this is best accomplished with least risk to the kidney by the arsenical preparations rather than the heavy metals.

In syphilitic nephritis, recovery is usually so complete that further antisyphilitic treatment may proceed routinely, as in uncomplicated cases. The proper procedure in an associated nephritis due to other causes will be dealt with in a subsequent paragraph.

Fever —In not a few individuals with early syphilis, especially those with pustular syphilides, there is fever, often slight, but sometimes ranging as high as 39 4–40°C (103–104 F) This is not a contra-indication to

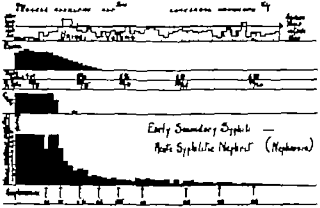


FIG. 29.—*U 43,872. Acute syphilitic nephritis (nephrosis) associated with early secondary syphilis. Cure of renal lesion by arsphenamine.*

Colored female, aged 16. Sore throat and skin rash for 1 week, edema of face, neck, and legs for 1 day On admission, chancre of cervix, macular syphilide, and papulo-erosions of buccal mucosa present, but not recognized for 1 week. *T pallida* demonstrated May 17 Blood Wassermann positive.

In addition, generalized edema, oliguria, tremendous proteinuria (40 grams per liter), low plasma protein, inversion of albumin/globulin ratio. No nitrogen retention (NPN 26–36 throughout illness) normal to high phthalein excretion (75–83 per cent) no anemia. Urea clearance 45 per cent on admission, rising to 62 per cent on discharge.

Note after arsphenamine —Prompt diuresis and loss of edema, immediate disappearance of casts, striking decrease in proteinuria (urine now normal, 2 months after discharge) return of plasma protein and A/G ratio toward normal. No harmful effect from arsphenamine.

During subsequent observation (July–October 1932) and further treatment, all evidences of renal damage have disappeared. The patient is completely well.

immediate and energetic treatment, which may proceed according to the usual routine. There may be a further rise in temperature for 12–24 hours after the first arsenical injection (Herxheimer reaction) but there is usually a prompt and rapid fall to normal thereafter

Malignant syphilis —Fortunately malignant syphilis is becoming so infrequent that even in a large clinic only a rare example is seen. The only feature associated with it which may require special management is secondary anemia. This usually improves rapidly as soon as specific treatment is started and lesions heal If it does not, liver should be added to the diet, and iron and ammonium citrate crystals, 0.25 gm. three times a day after meals, should be given in addition. Antisyphilitic treatment should be energetically pushed. Should the routine chemotherapeutic agents

prove ineffectual, fever treatment should be resorted to at once (cf page 222) We have never seen a patient such as the one reported by Wile, whose extensive malignant lesions failed to heal and in whom death occurred in spite of treatment.

Early neurosyphilis —The incidence of clinical signs of neurosyphilis (usually acute syphilitic meningitis, or isolated cranial nerve palsies without much meningeal reaction) in untreated early syphilis is low (about 0.5 per cent) Treatment should be energetically pushed from the outset, *without fear of a Herxheimer reaction. Further* details are provided in Chapter XXIV

The management of early syphilis associated with other diseases Pulmonary tuberculosis —The association of the two major infections tuberculosis and syphilis, is comparatively common It is an old observation that in patients with both diseases antisyphilitic treatment often results in a flareup or spread of the tuberculous lesion. Petersen and Hecht have provided an interesting, if somewhat hypothetical, discussion of this phenomenon. It is generally accepted but not proved, that all the drugs, particularly the iodides, used in the treatment of syphilis exercise some degree of non-specific resolving effect on granulomatous tissue in general and that if this occurs in tuberculosis, especially pulmonary tubercle bacilli may be freed from their surrounding zone of *protective inflammatory reaction with local spread or even general dissemination.* Bloch, on the other hand feels that this is not the case even with the iodides and that the activation of pulmonary tuberculosis following their administration occurs through a different set of circumstances He feels that they liquefy the sputum. This makes its aspiration easier and thus favors the bronchogenic spread of tuberculous infection. Unfortunately as pointed out by Padget and Moore and by Guild and Nelson there has been no collaboration between the expert in syphilis and the expert in tuberculosis in the study of this problem. Consequently no study so far is beyond criticism by one group or the other Nevertheless there is no *doubt that energetic treatment for syphilis may not only* precipitate general dissemination of the infection in an individual with acute pulmonary tuberculosis but may also cause activation of an apparently quiescent focus. We have seen at least a dozen examples of both these occurrences.

The physician's fear of antisyphilitic treatment under these circumstances depends on whether his experience is more largely in the field of tuberculosis or of syphilis. Our own reaction is one of wholesome respect for the danger Habliston, who has a large experience with tuberculous patients, has seen no ill results from antisyphilitic treatment carried out under conditions of sanatorium care. *However* as pointed out by *Guild* and Nelson the treatment of syphilis in patients in a sanatorium is apt to be routinized without regard to the type of either of the co-existing diseases. The difference in attitude lies largely in the fact that in the syphilis clinic, treatment is likely to be very intensive as compared to the relatively mild antisyphilitic measures used by the tuberculosis expert.

When active pulmonary tuberculosis is associated with a recent syphilit-

is infection, the physician must consider a number of factors—(a) both diseases are a menace to the public health, tuberculosis more than syphilis, since the infectiousness of the latter by all ordinary contacts except by the close personal relationship of sexual intercourse or kissing may be abolished within a few days after the start of treatment (b) tuberculosis is more likely to be immediately fatal than syphilis which if it kills at all, probably will not do so for 10–30 years (c) treatment for tuberculosis is primarily rest, both of the patient and of the affected organ, to promote isolation of the bacilli and to accelerate the formation of connective tissue defense (d) treatment sufficiently intensive to accomplish radical cure of syphilis is likely to do irreparable harm from the standpoint of tuberculosis.

Under these circumstances, the best procedure to adopt is to arrange as promptly as possible for sanatorium care and to manage the syphilitic infection from the standpoint of the healing of lesions and the prevention of infectious relapse. Small doses of neoarsphenamine (0.3–0 45 gm) or mapharsen (0.03–0 04 gm) separated by courses of intramuscular bismuth in half doses (0 1 gm.) will accomplish these results without materially disturbing the tuberculous process. *Iodides should be avoided at all times.*

Rheumatic heart disease —The association of rheumatic heart disease with early syphilis has a double significance. If the valvular lesion is aortic insufficiency it is essential to note its presence and its rheumatic etiology, since otherwise its discovery in later years will almost certainly lead to its erroneous designation as syphilitic. We have seen at least six patients with rheumatic aortic regurgitation in association with primary or secondary syphilis and in one or two of these the lesion has subsequently been mistakenly classified as syphilitic by other competent observers. This is of course important to the patient both as to prognosis (syphilitic aortic lesions are far more immediately dangerous to life than the rheumatic variety) and as to treatment.

In all patients with rheumatic heart disease and associated early syphilis, the immediate problem is the evaluation of the severity of the cardiac lesion. If compensation has not been lost, if cardiac reserve is adequate, and the patient seems likely to have long years of life before him, the syphilitic infection must be treated as energetically as is consistent with safety Patients with rheumatic cardiac lesions tolerate the arsenical drugs much better than do those with an apparently equivalent extent of damage due to syphilis The arsenical drug employed had better be neoarsphenamine or mapharsen than arsphenamine, however because of their lower toxicity Heavy metals may be used as in normal patients, since they exert no deleterious effect on the heart.

If on the other hand the patient has had one or more attacks of congestive heart failure if his cardiac reserve is low and if the prognosis from the standpoint of the cardiac lesion is so bad as to suggest a fatal outcome within a few years, or a life of chronic invalidism the problem as to syphilis consists only of sufficient treatment to heal infectious lesions, to prevent infectious relapse and thus to protect others. Small doses of neo-

arsphenamine (0 1–0.3 gm) or mapharsen (0 02–0 03 gm) and mercury by inunction, are all that is necessary

Essential hypertension —This condition, becoming so common in American patients is not a contra-indication to the energetic treatment of early syphilis. Such patients may be treated as intensively as normal individuals the only added precaution necessary being a frequent (monthly) examination of the urine. This is desirable to guard against the production of renal irritation and functional damage in kidneys already anatomically affected by arteriolar sclerosis.

Diabetes mellitus —The co-existence of this disease with early syphilis is also not a contra indication to energetic treatment. The diabetes should be brought and maintained under control as rapidly as possible by diet and insulin if necessary It is rarely if ever due to syphilis (no examples of syphilitic diabetes have been observed in our clinic), and treatment for syphilis has no effect upon the course of the metabolic disease beneficial or otherwise

Exophthalmic goitre —The association of syphilis with this condition calls for a judicious combination of surgical judgment and syphilotherapeutic skill. The thyroid disease is of more immediate importance than the syphilitic infection. Bed rest, iodine (administered in small doses as Lugol s solution for the exophthalmic goitre, not in large doses as potassium iodide for syphilis) and operation should be carried out as promptly as possible. Until convalescence is complete, small doses (0.1–0 45 gm.) of neoarsphenamine or (0 02–0 03 gm.) mapharsen should be given at 5–7 day intervals. Later after recovery more energetic routine treatment may be undertaken. Patients with Graves' disease and a high basal metabolic rate react badly to antisyphilitic drugs.

Nephritis present before or occurring during treatment —When albuminuria and cylindruria are present before treatment in a patient with early syphilis the problem is to determine first, to what extent renal function is impaired and second whether the lesion is due to syphilis or to some other cause. As we already pointed out, urinary abnormalities are not infrequent in early syphilis. Kidney function tests require time for their performance It is important to start antisyphilitic treatment at once, both for the sake of the patient and the public health. This may be done with safety pending the outcome of further study of the patient, by means of small doses of an arsenical preparation. Arsphenamine 0 1 gm., neoarsphenamine 0 15 gm. or mapharsen 0 02–0 03 gm. may be given to individuals with advanced non-syphilitic nephritis without danger and such doses may be repeated at 2–4 day intervals. If the renal lesion is due to syphilis this form of treatment will be productive of material improvement within 10 days to 2 weeks. If no such improvement occurs, a search for other possible causes of renal damage must be instituted. In acute hemorrhagic (non-syphilitic) nephritis, foci of infection should be searched for and extirpated when found. Antisyphilitic treatment should be carried on with minimum doses of the arsenicals (no heavy metal) until the outcome of the associated acute illness and the degree of permanent residual renal damage is clear

In patients with an associated non-syphilitic chronic nephritis the character and intensity of antisyphilitic treatment will be measured by an estimate of the probable prognosis of the renal lesion and the extent of damage to kidney function. Whether an attempt at radical "cure" is justified is based on the patient's probable life expectancy in view of the nephritis. With only moderate damage to kidney function the arsenicals are well tolerated in average therapeutic dosage, and of the two heavy metals bismuth is better tolerated than mercury, which should not be used at all in such patients.

Routine urine examinations during antisyphilitic treatment—Evidences of renal irritation from antisyphilitic drugs may appear during treatment. The risk of this was much greater before the introduction of bismuth, when mercury was given to every patient, often by the dangerous method of the intramuscular injection of insoluble mercurial salts. Various texts advocate the weekly examination of the urine in all patients undergoing antisyphilitic treatment. Under modern conditions we believe this is entirely unnecessary and that it suffices to repeat urine examinations every 2–3 months. If albumin and casts appear in considerable quantity in a previously normal urine treatment should be temporarily suspended. A trace of albumin and a few casts do not contra-indicate further treatment. If due to the drugs administered the urinary abnormalities will usually disappear promptly whereupon treatment may be cautiously resumed after a rest interval of one month. Since mercury has been so nearly completely supplanted by bismuth, evidences of marked renal irritation due to treatment are becoming almost non-existent.

The sulfonamides and antisyphilitic treatment—The similarity between the more severe toxic reactions (jaundice, dermatitis, etc.) caused by the sulfonamides and the arsphenamines and mapharsen raises the question of the safety with which these preparations may be used simultaneously in patients with chancroid, lymphogranuloma venereum or gonorrhea associated with syphilis. In 150 patients with both gonorrhea and syphilis, 25 of whom had early syphilis and consequently were treated intensively Kemp noted no increase in untoward reactions to either group of drugs. This corresponds to the experiences of others and is a fortunate circumstance in view of the large number of patients who have more than one venereal disease, whether contracted simultaneously or otherwise.

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Chapter XV

THE PRINCIPLES OF TREATMENT OF LATE SYPHILIS

Although the principles of individualization of treatment of late syphilis are frequently discussed throughout this monograph, we dignify them here for the sake of emphasis, with a chapter heading of their own. We have already pointed out (Chapters XII and XIII) that while in early syphilis one may treat the disease, in late syphilis one must treat the patient.

In contrast to the uniformity of distribution of organisms and lesions and of immune response in early syphilis late syphilis is characterized by a wide diversity of location and extent of lesions involving almost any structure in the body often disturbing vital functions and also by wide individual variations of the degree of resistance against infection. Some infected patients, highly resistant, go through life with no outward signs of disease others develop one disfiguring or crippling lesion after another finally dying of syphilis. However no matter what degree of protective resistance against the invading organism in his own tissues the patient may develop it is sufficient in the majority of instances to protect him from fresh organisms coming from without, and it is assumed, on the grounds discussed in Chapter II that this resistance cannot be significantly altered by treatment, no matter how intense or prolonged. It is further assumed, for what seem to be adequate reasons (Chapters II and III) that in contrast to the state of affairs in early syphilis, a long-standing infection in man cannot be eradicated, biologic cure cannot be achieved by means of any form of treatment so far developed.

If the biologic cure of late syphilis is unattainable, what is the purpose of treatment? Obviously its first aim is symptomatic relief the restoration when possible of anatomic normality or if this is impossible of functional normality When even this latter cannot be achieved (as in cardiovascular syphilis) the immediate aim of treatment is to stop the progress of the lesion. Fortunately for most patients, symptomatic relief the healing of lesions, is readily accomplished by relatively small amounts of treatment. Clinical experience, however shows clearly that unless treatment is carried further relapse—the appearance of new lesions in the same or a different organ—or progression—a renewal of the inflammatory or degenerative process in the original incompletely healed lesion—are likely to occur

The second aim of treatment, therefore, is to consolidate the gain to maintain the patient in good health, free from progression or relapse, for the balance of his lifetime. All other aims (except that of control of infectiousness) are subsidiary This is, of course, the same ultimate goal as in early syphilis an important difference between the early and late stages of the disease is that in the former the distance to the goal and the point at which it is ultimately reached are measurable, at least partly in terms of

THE LABORATORY DIAGNOSIS OF LATENT SYPHILIS REQUIRES

1. Presumptive or actual opportunity for infection.
2. Absence of possible causes for biologic "false positive" blood tests.
3. Exclusion of technical error in blood serologic tests by
   - (a) Verification through repetition
   - (b) Performance in laboratory of known excellence
   - (c) Avoidance of reliance on supersensitive techniques.
4. Confirmation may be necessary by
   - (a) Recheck by several standard techniques
   - (b) Recheck in different laboratories
   - (c) Recheck by special techniques
     - (1) Spirochetal complement fixation test
     - (2) Kahn "verification test."
5. Negative results of C.S.F examination.

FIG. 31

nervous systems and *of the special senses, has revealed no lesions attributable* to the disease. The diagnosis rests therefore, either on repeatedly positive serologic tests of the blood or if they are negative, on a clear cut history of infection inadequately treated or (in the female) on the birth of a syphilitic child (Figs. 30 and 31) For practical purposes, those patients with apparently latent syphilis but with abnormal spinal fluids must be separately considered.

So far the most important clinical contribution to the problem of latency has been recognition of the fact that about 15 per cent of patients with apparently latent syphilis actually have asymptomatic neurosyphilis *A priori* one expects the prognosis in such patients treated or untreated, *to be different from that for the group with negative spinal fluids* and this is actually the case. Indeed as appears from Fig 32, the difference in probable outcome, so far as the ultimate development of clinical neurosyphilis is concerned is so great that all patients with abnormal spinal fluids must be excluded from the category of latency A final diagnosis of "latent syphilis" is therefore not permissible unless examination of the spinal fluid has been performed and is normal.

Further clinical advances tending to remove patients from the diagnostic classification of latent syphilis to a better defined anatomicopathologic group must await the development of general medical progress with its refinements of clinical and laboratory approach. The most promising *field for immediate study lies in the earlier diagnosis of cardiovascular* syphilis It cannot be too strongly emphasized that the diagnosis of latent syphilis depends on negative physical evidence and that the more thorough and searching one's methods of clinical examination become, the more frequently lesions of late syphilis will be recognized and the fewer patients will be admitted to the classification of latency

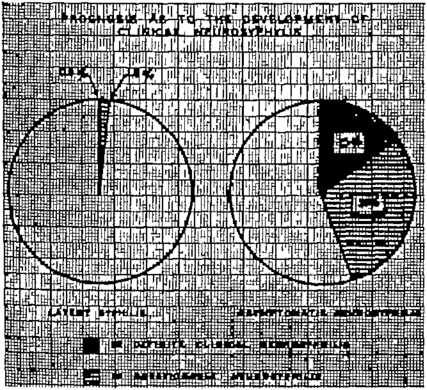


Fig. 32

The frequency of latent syphilis—The importance to the practitioner of a thorough understanding of the problems of latent syphilis is obvious from the fact that at least one of every three syphilitic patients whom he sees will be in the latent stage of the disease. The frequency of latency in a large syphilitic population is shown in Fig 33 based on Turner's study of 10 000 patients in the Johns Hopkins clinic. One-third of all males and nearly one-half of all females presenting themselves for treatment had no physical evidence of infection. The proportion of latent syphilis is now even higher since more widespread use of routine serologic testing.

The relationship of symptomless infection to latency—Forty three per cent of our patients with latent syphilis could give no history of infection In part, this may be due to the fact that lesions of early syphilis did occur but were so insignificant or transitory as to be remembered only for a short time fading from memory because of their very insignificance. This does not suffice however to explain the situation entirely Symptomless infection in man not only occurs but is probably frequent. The importance of this fact lies in the facts that these individuals are recognized as syphilitic only by the accident of routine serologic testing when some other disease makes medical advice necessary or by the development of

some lesion, often crippling of late syphilis and that, in some instances at least, and though themselves free from obvious lesions of early syphilis they may act as carriers and transmit the disease to others.

Symptomless infection is of obvious importance in latent syphilis in two ways first, the patient's failure to react with the usual tissue outbreak

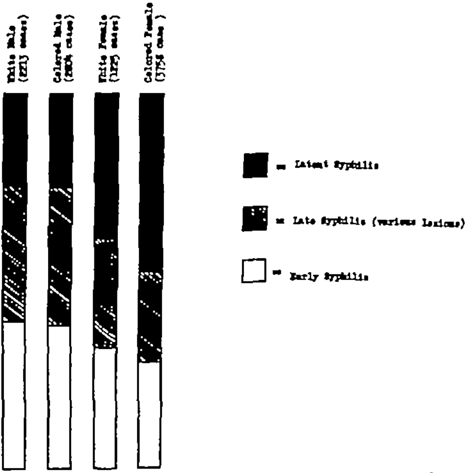


FIG. 33.—The relative incidence of latent, late and early syphilis by race and sex (after Turner)

Note the much higher incidence of latent syphilis among women.

of secondary syphilis may indicate the probability of a serious outlook for the future*; second, symptomless reinfection as well as symptomless original infection, may occur

Furthermore the considerable group of patients with silent infections constitutes the main indeed the only insurmountable impediment to the

* Many clinical and some experimental observations indicate that lesions of late syphilis are less likely to appear in patients or animals who have undergone an extensive early tissue reaction (profuse secondary eruption, for example) and more likely to develop in individuals in whom the early tissue reaction was slight or absent.

realization of the medical ideal of eradication of syphilis as a major infection by means of the universal application of early diagnosis and early adequate treatment. They are the justification if any were needed, for the syphilologist's insistence on the extension of routine serologic tests of the blood in medical practice.

The pathology of latent syphilis and its relationship to treatment —The pathology of latent syphilis has been studied extensively by Warthin. He has emphasized that the harmony between host and parasite is more apparent than real, that beneath a serene outward surface, slow fibrotic changes are occurring in important viscera, and that syphilis can be said to be latent only in the sense that the pathologic changes present and in process of development are inappreciable by our relatively gross clinical methods of approach. Warthin finds pathologic alterations in latent syphilis with great frequency in various organs ranging from 30 per cent for the liver to 80 per cent for the testes and 90 per cent for the aorta. He also lays *stress on the presence of these changes in the tissues* of treated and presumably cured syphilitics, as well as in those untreated

A review of the necropsy material of the Johns Hopkins Hospital does not confirm Warthin's findings. Among 12,000 autopsies Mohr Hood and Katzenstein found only some 150 instances in which the diagnosis of syphilis, not clinically recognized during life depended solely upon post mortem findings. This figure is certainly high since in some instances death occurred before complete clinical examination of the patient was possible. Conversely there were approximately 650 patients known to have syphilis during life who showed no necropsy evidence thereof a finding in direct contradiction of Warthin's data.

TABLE 43

PATHOLOGIC LESIONS FOUND IN 501 CASES OF SYPHILIS (417 MALES, 84 FEMALES) AMONG 1675 NECROPSIES IN PATIENTS OVER 25 YEARS OF AGE

(Modified after Warthin)

Tissue or organ	Total examined	Number with definite lesions of syphilis	Percentage with syphilitic lesions
Spinal cord	68	31	45.5
Brain	234	90	38.4
Meninges	242	207	85.5
Aorta	490	441	90.0
Heart	499	329	65.9
Liver	483	145	30.0
Adrenals	473	192	40.5
Pancreas	491	170	34.6
Testes	401	321	80.0

Leaving to one side the controversial aspect of Warthin's work, and the inability of other perhaps less meticulously accurate, pathologists to repeat it certain comments may be made as to the validity of the con-

clusions which have been drawn from it. It is unfortunate that nowhere does Warthin provide information as to what proportion of his patients, described as clinically non recognizable latent syphilitics were actually diagnosed as syphilitic during life either on clinical or serologic grounds The absence of these data leads to the justifiable comment that the material may contain patients whose infection was actually clinically apparent and not latent, and invalidates the conclusions as to the possibility of cure. It is unfortunate also that nowhere does he provide information as to the extent of pathologic damage to tissues, nor the details of treatment received by the patient during life, nor the cause of death. It is fair to assume on the basis of necropsy experience the world over that most of them did not die of syphilis.

The prognosis of latent syphilis —Syphilis does not always maim or kill the treponeme may be so far as anyone can tell from clinical study a perfectly harmless saprophyte. This factor is one which must be given due weight in any consideration of the problem of treatment of latent syphilis. Assuming that the disease has existed for at least four years so that the patient's own defense mechanism has had time to become firmly established that searching physical examination has revealed no lesions especially in cardiovascular or central nervous systems, and that the cerebrospinal fluid is negative one is probably justified in predicting that a given patient if he receives no treatment at all is likely to meet the fate shown in Table 44 * At best, it is probable that he has only about 1 chance in 4 of developing any serious trouble at worst not more

TABLE 44
THE PROBABLE OUTCOME OF UNTREATED LATENT SYPHILIS
(See text)

Outcome	Approximate percentage of patients in whom specified results may be expected to develop
Spontaneous "cure" (Blood tests and C.S.F negative no lesions)	25–35
Infection remains latent (Blood tests positive C.S.F negative no lesions)	25–35
Late syphilis (skin, mucosa, osseous)	10–15
Cardiovascular syphilis	10–15
Neurosyphilis	1– 2
Visceral syphilis, other than cardiovascular	0.5– 1

than 3 chances in 10 If lesions do occur there is probably not worse than an even chance that they will be incapacitating and cardiovascular involvement *is the chief serious risk which must be feared. As shown in* Chapter XXI the danger of the development of neurosyphilis (probably excepting only a more or less purely vascular involvement) is largely past

* These tentative figures are based on Bruusgaard's fundamental study of the course of untreated early syphilis, as well as on our own observations

by the time true latency in the sense in which we have used the word, is achieved

The age of the patient in relation to treatment —The patient's age is a vital issue in determining the kind and amount of treatment, if any which should be administered. Given a patient who has passed the age of sexual activity so that he no longer exposes others to the infection and whose own probable life expectancy is only 10 or 15 years, the risks of treatment may well be greater than the risks of syphilis. It is of course not possible to set an age limit past which treatment should not be given or its intensity lessened each patient presents an individual problem to be solved only after consideration of his physical and social status Obviously however the grandmother is a different case from the young married woman, the man of 65 from the boy of 20

Infection versus disease in syphilis and tuberculosis —It is interesting and important to draw the parallel between infection and disease in syphilis and tuberculosis. There is general agreement, on the basis of routine tuberculin testing and necropsy studies that approximately 80–90 per cent of all adults have developed tuberculous infection. The incidence of tuberculous disease, i.e. the number of patients made ill by the infection, is more difficult to determine but probably does not exceed 3–6 per cent of the adult population. Thus, there is not more than about one chance in 15 that tuberculous infection will result in actual disease. With syphilis the situation is different. As nearly as can be estimated about 10 per cent of the adult population will at some time become infected with syphilis. Disregarding as unimportant the lesions of early syphilis, the best available modern studies indicate that of the infected individuals, if untreated, approximately 50 per cent will develop some late lesion and that in about 25 per cent the late lesion will be partly or wholly incapacitating or fatal. With only one chance in two of freedom from disease, instead of the one chance out of 15 in tuberculous infection, it is obvious that laboratory evidence of syphilitic infection, the positive serologic blood test of latent syphilis cannot be lightly dismissed It must be interpreted to mean not only the certainty of infection, but also the probability of disease. A positive serologic test is a much more portentous finding than a positive tuberculin test. If the incidence of syphilitic infection were as high as that from tuberculosis, an accident from which we are saved largely by the fact that the treponeme dies as soon as it dries, the consequences to mankind would be devastating.

The reasons for the treatment of latent syphilis progression infectiousness —Enough has been said as to the pathology and prognosis of latent syphilis to indicate that under ordinary circumstances, treatment should be given Perhaps the importance of these two factors can be emphasized more strongly by pointing out that nearly every patient with a late lesion of syphilis has passed through the stage of latency and that had his infection been recognized at that time the appearance of the late lesion might have been forestalled.

The potential infectiousness for others of patients with latent syphilis is another reason for instituting treatment. The chances of such an occur

with apparently equally satisfactory results and certainly with less discomfort to patients.

The choice and amount of heavy metal —Even the scanty comparisons between bismuth and mercury available in early syphilis are lacking in latent syphilis The same considerations which impel the choice of bismuth in early syphilis however seem to us operative also in latent syphilis and in our clinic it has almost completely replaced mercury As to the amount to be administered numerous straws in the wind in the C C G studies indicate that the results in latent syphilis are better if relatively much more heavy metal is employed than in early syphilis Indeed, the best results were obtained at one of the clinics which employed relatively little of the arsenical preparations but repeated courses of a

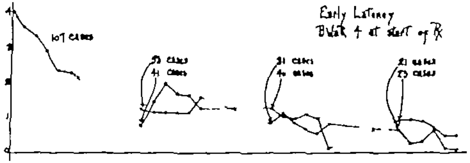


FIG. 35.—The composite Wassermann curve in 107 patients with early latent syphilis (blood Wassermann completely positive at start of treatment) intermittent *versus* continuous treatment.

In this and subsequent similar charts the solid lines indicate periods of arsphenamine therapy the dashes, periods of heavy metal therapy or intervals without treatment. The solid dots indicate patients treated continuously· the open circles, patients treated intermittently

heavy metal, often alternating bismuth and mercury over long periods of time In the latter part of the treatment of individual patients this particular clinic often gives a course of heavy metal once or twice a year for 3 5 10 years or even longer the interval between courses being occupied by rest periods The disadvantage of such a treatment scheme however is obvious. In the average clinic it is difficult to keep patients under observation for long periods even after treatment has been discontinued. It is still more difficult to get them to return at fixed intervals for treatment, particularly when they are and have been for a long time completely asymptomatic. In adopting a treatment scheme for latent syphilis it is important to attempt to complete treatment as expediently as the individual case permits

According to Diseker s study of our own material, however the ultimate results of treatment assuming that the optimum dosage of arsenic has been given are as *satisfactory when a minimum of 20–24 doses of* bismuth are given in conjunction as with larger amounts. This holds good apparently both for early and late latency

Continuous versus intermittent treatment in latent syphilis—The time necessary for the development of true latency and of maximum resistance is variable in individual patients but is probably always complete within four years. After the development of resistance, it is likely that treatment, adequate or inadequate will not disturb the immunologic relationships already established. Under these circumstances the necessity for continuous treatment is no longer so imperative as in early syphilis. Rest periods do no serious harm. Thus *a priori* reasoning is borne out by the studies of the C.C G A satisfactory clinical outcome, clinical and serologic relapse, and seroresistance were approximately equal in groups of patients treated continuously or intermittently

The course of the Wassermann curve during treatment is confirmatory of this statement. In patients with early latent syphilis (i.e. of less than

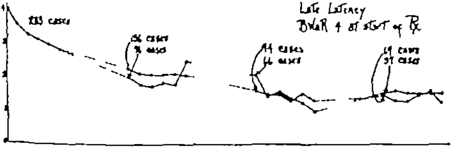


FIG. 26.—Intermittent *versus* continuous treatment The composite blood Wassermann curve in 233 patients with late latent syphilis (blood Wassermann completely positive at the start of treatment)

4 years duration) there is apparent the same tendency to serologic relapse during rest intervals as in early syphilis (Chapter XIII) indicating that in these patients resistance or immunity is not as yet thoroughly developed. In late latency (of more than 4 years duration) this phenomenon is absent, and the course of the curves during intermittent treatment is nearly identical with that during continuous treatment.

Whether continuous treatment should be as rigorously insisted upon as in early syphilis or whether an occasional rest interval may be permitted depends on the approximate duration of infection. If a history is lacking, an estimate of this may often be made on the basis of such collateral factors as the patient's age, history of recent initiation into sex activities etc. If the infection is of less than 4 years duration, the patient should be treated in all respects as if he had early syphilis.

Factors influencing the outcome of treatment in latent syphilis—Aside from treatment three factors materially influence the outcome of treatment in latent syphilis These are (1) the duration of the infection (2) the duration of observation and (3) the sex of the patient and the occurrence or non-occurrence of pregnancy after infection or during treatment.

The influence of duration of infection—This is the most important of all extraneous factors. The earlier the infection is recognized and

treatment started, the better the chances of a satisfactory outcome of treatment. This is clearly shown in Table 45 "Satisfactory results" indicate the completion of treatment and of a probationary period, varying

TABLE 45

THE DURATION OF INFECTION AS INFLUENCING THE OUTCOME OF TREATMENT IN LATENT SYPHILIS
(Material of C.C.G.)

Stage of latency	Total patients	Percentage with		
		Satisfactory results	Unsatisfactory results, all types[1]	Still under treatment[2]
Early	514	50 8	35 7	15 6
Late	1197	33 7	52 5	15 5

[1] Clinical and serologic relapses, seroresistance deaths.
[2] Progress to date such as to indicate that satisfactory outcome will ultimately be obtained

from a few months to many years during which there was no physical evidence of clinical progression or relapse and all laboratory tests of blood and spinal fluid remained negative. The unsatisfactory results in both groups are largely serologic rather than clinical since only 4.0 per cent of patients with early latency (nearly half of these with relapses of the early infectious type) and only 4.8 per cent of those with late latency developed clinical relapses.

The influence of the duration of observation.—Table 46 indicates the ultimate outcome as compared with the total duration of

TABLE 46

RESULTS OF TREATMENT IN LATENT SYPHILIS ACCORDING TO THE TOTAL LENGTH OF OBSERVATION
(Material of the C.C.G.)

Duration of observation	Total cases	Percentage of patients with					
		Results satisfactory	Results unsatisfactory			Still under treatment doing well	Dead
			Clinical relapse	Serologic relapse	Sero-resistant		
Less than 2 years	923	15 2	2 4	9 4	51 0	22 0	1 2
2–5 years	686	46 0	4 5	10 3	31 6	8 0	1 7
5–10 years	289	60 6	5 2	10 8	20 9	3 1	1 1
More than 10 years	40	85 0	2 5	5 0	7.5	—	—

observation, regardless of the total amount of treatment given. It appea
to show quite clearly that the longer one follows one s patients with later
syphilis the higher the proportion of satisfactory results. In patien
followed for less than 2 years only 15 per cent had achieved and mai
tained clinical quiescence and serologic negativity and in those followe
for 2–5 years, 46 per cent, for 5–10 years, 60 per cent, and for more than 1
years, 85 per cent.

The gain in satisfactory results in successive years is obviously at th
expense of two other groups i.e. seroresistant patients who diminis
progressively from 51 to 7.5 per cent, and those still under treatment. W
have already provided an estimate (Table 44) that satisfactory resul
(clinical quiescence and persistent serologic negativity) would occur i
25–35 per cent of patients with latent syphilis who received no treatmen
at all, that an additional 25–35 per cent would remain free of lesions bu
would retain positive serologic tests of the blood, and that about 20–3
per cent would ultimately develop some lesion of late syphilis. These est
mates were intended to cover a lifetime of observation, as in Bruusgaard
material and it may be claimed with justice that patients followed fo
only 10–15 years have not yet reached a point permitting comparison wit
the hypothetical untreated group. However assuming that the presen
status is maintained in the C.C G material, the probability of sati
factory outcome has been increased from 35 to 85 per cent the percentag
of serologically positive but clinically quiescent cases reduced from 35 t
7.5 per cent and the probability of progression or relapse reduced from 20
30 to 2–5 per cent. It is a noteworthy fact that the incidence of clinic
relapse is approximately the same in patients followed for 5 years o
longer as in those followed for a shorter period though the average amoun
of treatment given to all patients observed for 2 years or longer is th
same. Freedom from progression or relapse brought about by treatmen
seems, therefore, to be relatively permanent, at least within the limits of
10 year observation period. This gain is certainly due to treatment, and
certainly worth while.

The influence of sex and of pregnancy —Since syphilis is a milde
disease in women than in men, one would naturally expect the results
treatment to be somewhat better in females when the comparison
actually made the differences in outcome are not marked. In one respec
however the female has the advantage of the male —she is able to ava
herself of the therapeutic benefits of pregnancy That this benefici
effect actually exists is suggested by the material of the C.C G

In Table 47 is provided a comparison of the ultimate outcome in 2
women who were pregnant on admission to the various clinics or who b
came pregnant during treatment with 303 women who had never bee
pregnant. Satisfactory results were obtained in 42 per cent and ser
resistance was observed in only 18 per cent of the pregnant as compare
with 29 per cent and 42 per cent, respectively of the non-pregnant grou
So far as the female patient herself is concerned, therefore, pregnanc
after infection with syphilis appears to exercise a distinctly benefici
effect. It may actually be advised as a therapeutic measure provided du

TABLE 47

RESULTS OF TREATMENT IN LATENT SYPHILIS. THE APPARENT INFLUENCE OF PREGNANCY ON THE ULTIMATE OUTCOME
(Material of C.C.G.)

	Total cases	Percentage of patients showing				Still under treatment, doing well	Dead
		Results satisfactory	Clinical relapse	Sero-relapse	Sero-resistance		
Females pregnant on admission or during treatment	283	42.4	4.2	9.5	16.4	25.8	1.4
Females never pregnant	303	29.7	4.3	9.6	42.2	15.2	0.3

Including 14 pregnant and 47 non-pregnant females observed for less than 1 year

consideration is given to the possible birth of a syphilitic child, and due treatment precautions (Chapter XXVI) undertaken during pregnancy to prevent this disaster.*

The control of infectiousness by the treatment of latent syphilis.—To measure the control of infectiousness by sex contact in patients treated for latent syphilis is a manifest impossibility. Reasoning by analogy from early syphilis it is probable that potential infectiousness by all ordinary means except the remote possibility of seminal infection is eliminated.

More readily appreciable, however, is the effect of treatment in preventing the development of congenital syphilis in the offspring of women with latent syphilis. The contrast in the outcome of pregnancy before and after treatment is amply shown by the material of the C.C.G. shown in Table 48. The prospect of a normal baby is increased from 16 to 65 per cent as a result of treatment.

TABLE 48

THE OUTCOME OF PREGNANCIES IN WOMEN WITH LATENT SYPHILIS, BEFORE AND AFTER TREATMENT
(Material of the C.C.G.)

	Pregnancies	Children born alive, healthy percentage
Pregnancies before treatment	1467	16.9
Pregnancies during or after treatment	230	65.2

* Diaker's more elaborate and careful study indicates, however, that the more favorable outcome of treatment in women than in men probably depends on other factors than pregnancy.

The nature of relapse or progression in latent syphilis —In the material of the C C G., progression or relapse was observed in 4.8 per cent of the patients studied. The majority of these occurred in patients who had had 20 or less injections of an arsphenamine. In a third of the patients, the relapse was benign in type and inconsequential so far as the patient's health was concerned. About a third each of the relapsing patients developed cardiovascular or central nervous system syphilis (no instances of tabes or paresis) but here also the lesions were mild and rarely incapacitating. This is to be interpreted as due partly to the degree of development of the patient's own resistance partly to the added protection afforded by treatment. It indicates that a patient with latent syphilis may be assured with reasonable certainty that if he submits to a moderate regime of treatment, he may be promised 19 chances out of 20 of freedom from clinical evidence of disease in the future and that if lesions do develop they will rarely be incapacitating.

Clinical improvement in latent syphilis —It is a common experience for a patient to report, a few weeks after starting treatment that although he had not been conscious of feeling badly before treatment, he now feels very much better He has more energy tires less easily has an improved appetite, sleeps better such vague discomfort or malaise as he may have had has disappeared. Indeed he often looks better he gains a little weight, his color is improved. This change is more than the tonic effect of treatment experienced by non-syphilitic patients it represents, apparently genuine improvement in the systemic infection, and is a sustained gain.

Serologic response in latent syphilis during treatment —In Fig 37 appears the course of the composite Wassermann curve over a period of at least one year of treatment (four courses of an arsphenamine)



FIG. 37 —The composite Wassermann curve in latent as compared with early secondary syphilis during prolonged continuous treatment.

in 52 patients with latent syphilis as contrasted with 50 patients with early secondary syphilis. These cases are selected in the sense that each received *continuous* treatment the interim between arsphenamine courses being completely filled by the use of a heavy metal with or without potassium iodide The degree of serologic response during the first arsphenamine course is much less in latent than in early syphilis. In both groups there is continued progression toward negative during the first course of heavy

metal (prolonged arsphenamine effect?) Thereafter however the course of the serologic tests in early syphilis continues slowly downward until almost complete negativity is reached by and maintained after the third arsphenamine course while in latent syphilis any further treatment after the first heavy metal course exerts only a slight and practically negligible effect on the serologic tests. In other words, so far as the composite curve in latent syphilis is concerned almost all of the serologic response to be expected occurs within the first 4 months of treatment thereafter further treatment has little effect.

This is accounted for, of course by virtue of the fact that in latent syphilis, serologic relapse (even during treatment) and seroresistance are frequent occurrences as compared with their incidence in early syphilis. About 35 per cent of all patients with late latent syphilis are persistently seropositive under any form of treatment. How shall these phenomena be interpreted and what practical bearing have they on the management of the patient?

The significance of serologic relapse and seroresistance in latent syphilis —In latent syphilis serologic relapse and probably also seroresistance are based on fundamentally different reasons than in early syphilis In the latter case treatment accomplishes simultaneous rapid destruction of organisms and reversal of serologic tests and prevents the development of immunity Cessation of treatment before destruction of organisms is complete may lead, because of the patient's lack of defense (1) to local multiplication of treponemes with local clinical relapse as in eye or nervous system associated with a relatively low incidence of serorelapse or (2) to redissemination of treponemes manifested by mucocutaneous or serologic relapse singly or together Under these circumstances the serologic test becomes positive before or during the relapse by virtue of the same mechanism of production of reagin which caused its original positivity

In late latent syphilis, however it is possible that most of the organisms seeded in the tissues at the original outbreak have already been destroyed by the development of the patient's own defense mechanism, which treatment affects little if at all. The early part of treatment accomplishes neither a wholesale destruction of treponemes nor (usually) rapid serologic reversal cessation of treatment short of sterilization is not accompanied by redissemination (extreme infrequency of secondary relapses) because of the patient's own immunity Serologic relapse is therefore, not on the basis of a fresh outpouring of reagin from the rapid remultiplication of organisms within the host. Instead it is possibly due to the fact that treatment depresses the reagin to a level which leaves the routine serologic tests on the borderline between positive and negative subject to variations in either direction for reasons not as yet clearly understood, but at least in part connected with the technique of the test (Fig. 38)

On this basis, serologic relapse in latent syphilis may mean simply that treatment has depressed the quantity of reagin in the blood to a point at which serologic tests are negative with routine amounts of serum by a relatively insensitive test, but still positive if the sensitivity of the test is

increased (cf page 526) Seroresistance may mean only that treatment has depressed the reagin level not quite so far and that even with the routine technique the test remains persistently positive. That this may be true is suggested by some as yet unpublished studies of our own on the use of a quantitative serologic technique in following treatment results

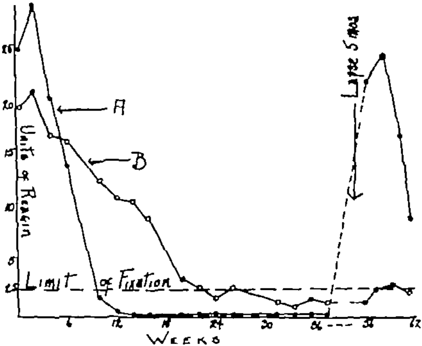


FIG. 35.—To illustrate possible variation in the mechanism of serorelapse in early as compared with late syphilis.

In patient A, the serologic response to treatment has been prompt reduction to complete negative (no reagin demonstrable in the blood) After a lapse in treatment of 5 months between the 30th and 56th weeks (indicated by the line of dashes) there is a serologic relapse of high titre. In the majority of cases, this is accompanied by clinical evidence of redissemination of organisms (clinical relapse)

In patient B, the reduction of the serologic tests by treatment is much slower and *never reaches the level of complete negative. The test vacillates above and below the* level of limit of fixation (2 5 units of reagin); below this level the 'routine' test is negative, above it, positive. Serorelapse, during treatment or after the lapse, is more apparent than real.

which show quite clearly that in late syphilis so-called seroresistant patients are divisible into two broad classes —(1) those in whom the test is originally positive with minute amounts of serum the titre being markedly but not entirely reduced by treatment until a constant low reagin titre is reached and (2) those with a relatively low reagin titre to begin with in whom treatment exercises little or no effect. Further progress in the study of the phenomenon of seroresistance depends on the prolonged use of the quantitative method of study

Further to understand the significance of seroresistance in latent syphilis, it is essential to study the ultimate clinical outcome in terms of progression or relapse in comparable series of patients with and without this phenomenon of serologic resistance. When this is done (Table 49) one

TABLE 49

COMPARISON OF THE INCIDENCE OF RELAPSE IN LATENT SYPHILIS IN PATIENTS SERORESISTANT VERSUS PATIENTS WHOSE SEROLOGIC TESTS REVERSE DURING TREATMENT

(After Diaker)*

	Total Patients	Infectious Relapse		Cardio-vascular		Neuro-syphilis		Multiple lat		Benign late		Total	
		N	%	No.	%	No.	%	No.	%	No.	%	No.	%
Seroresistant	646	2	.3	23	3.4	19	2.9			1	.2	44	6.8
Not Sero-resistant	535	3	.6	13	2.4	18	3.4	1	.2			35	6.5
Total	1181	5	.4	36	3.0	37	3.1	1	.1	1	.1	79	6.7

All patients followed for 5 or more years.

finds that the likelihood of relapse is no greater when the serologic tests remain positive than when they reverse to negative. It appears, therefore that *the seroresistant latent syphilitic is in no special danger because of his persistently positive test.*

In individual seroresistant patients it is a common experience to stop treatment after an arbitrary period of time (usually 2 years) and to find that during subsequent observation without treatment the test becomes spontaneously negative. This is probably the natural trend of events, since the incidence of seroresistance in latent syphilis progressively decreases with increasing periods of observation. Thus of patients followed for less than 2 years 51 per cent were seroresistant for 2–5 years 31 per cent for 5–10 years 21 per cent and for more than 10 years only 7 per cent.

Therefore, if the physician has examined his patient with sufficient care to be certain that he is dealing with latent rather than with cardiovascular or neurosyphilis he need not be alarmed over seroresistance or occasional serorelapse. Both are in all probability merely an index of the sensitivity of the serologic test employed. Indeed with further refinement of serologic technique, it becomes increasingly likely that so sensitive a test will be developed as to make it difficult if not impossible ever to obtain a negative result from treatment in late syphilis.

Suggested outline of treatment for latent syphilis—On the basis of the various considerations enumerated it is possible to plan a rational outline of treatment for latent syphilis capable of application to the average patient. Such an outline is suggested in Table 50. This provides for a little over a year of continuous treatment, during which a minimum of 24 doses of neoarsphenamine or mapharsen (to control infectiousness) and 28–30 doses of bismuth are given. Rest periods are not forbidden but should be limited to the latter half of treatment. This amount of treatment should be given regardless of serologic progress.

TABLE 50

SUGGESTED OUTLINE OF TREATMENT FOR LATENT SYPHILIS

1. Complete and thorough physical examination.

2. Routine test of spinal fluid before starting treatment, or as soon thereafter as possible.

3. If early latency (less than 4 years duration) use outline of treatment for early syphilis (Chapter XIII) *Treatment must be continuous!*

4. If late latency:

Weeks	
1–7	8 weekly doses neoarsphenamine 0.45–0.6 gm. or mapharsen 0.05–0.06 gm.
8–17	8–10 weekly doses bismuth
18–25	8 weekly doses neoarsphenamine, or mapharsen
26–37	12 weekly doses bismuth
38–45	8 weekly doses neoarsphenamine, or mapharsen
46–53	8 weekly doses bismuth
54–	Probation

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CHAPTER XVII

THE TREATMENT OF BENIGN (OSSEOUS MUCOCUTANEOUS) LATE SYPHILIS

FOR the purpose of this discussion benign late syphilis is defined as the allergic type with inflammatory (often gummatous) lesions involving structures not essential to the maintenance of life or vision In the vast majority of patients, such lesions involve the bones (periostitis, osteomyelitis, osteitis arthritis) the muscles or tendons (gummas of muscle synovitis) or the skin or mucous membranes (late nodular syphilides cutaneous or mucosal gummas) Ocular syphilis is purposely excluded from this discussion details concerning its treatment will be found in Chapter XX. In a few instances patients with the allergic tendency develop gummatous lesions of important viscera —liver spleen testes stomach and rarely gummatous lesions appear in cardiovascular or central nervous systems. These latter are also excluded from consideration here since the lesions involve vital structures. In effect then the discussion resolves itself into a consideration of late osseous and mucocutaneous syphilis lesions which, however much pain disfigurement, or temporary incapacity they may produce, rarely if ever kill the patient.

It has long been our clinical impression, unverified by definite facts, that the results of treatment in benign late syphilis, expressed in terms of ultimate outcome, were less satisfactory from both clinical and serologic standpoints than in late latent syphilis. This impression has been subjected to critical analysis in a study by Wasserman and Goodman of a large series of patients with late osseous or mucocutaneous syphilis from the Johns Hopkins clinic The clinical material is unselected except in the sense that all patients must have been under observation for 2 years or longer The following paragraphs are based on a survey of the first 200 of their patients.

The therapeutic problem —The physician who has read Chapter XVI, dealing with latent syphilis will recall that from that diagnostic category are excluded all patients in whom detectable lesions of any description exist, and that the diagnosis rests on anamnestic or serologic evidence only In benign late syphilis, this exclusion cannot be made, the patient complains primarily of his skin mucosal or bone lesions but he must be thoroughly studied to discover what other if any damage has been done by syphilis. The discovery of lesions elsewhere than in skin or bones may completely modify the plan of therapeutic attack. The extent of multiple involvement in our patients is presented in Table 51 Sixty four patients with late osseous and 63 with late mucocutaneous syphilis had no other clinically discoverable lesions In 36 of the former and 37 of the latter a total of 36.5 per cent, other lesions were present. The high incidence of late cutaneous syphilides in patients with bone syphilis and

TABLE 51

THE THERAPEUTIC PROBLEM IN BENIGN LATE SYPHILIS. THE ASSOCIATION OF SYPHILITIC LESIONS IN OTHER STRUCTURES

Patients in whom the presenting late lesion was	Total patients	Total with syphilitic lesions elsewhere	Number in whom were present associated syphilitic lesions of					
			Cardiovascular system	Central nervous system	Visceral	Mucocutaneous	Osseous	Ocular
Osseous	100	36[1]	13	13[2]	3[4]	9	—	—
Cutaneous	100	37[3]	7	11	1	—	19	5
Total	200	73	20	24	4	9	19	5

[1] In 2 patients, lesions of two other structures were present.

[2] In 6 patients, lesions of two other structures were present. Three of these patients had general paresis.

[3] In 1 patient, syphilitic hepatitis and splenitis in one, mediastinal gumma, in one, gumma of testis.

[4] In one patient, paroxysmal hemoglobinuria.

vice versa, is at once apparent this however has no bearing on treatment. Cardiovascular and neurosyphilis were slightly less frequent in patients with late cutaneous than with osseous lesions, but 10 and 12 per cent respectively of the total group showed clinical evidence of involvement of these vital structures. In 3 of the 4 patients with visceral syphilis the visceral lesion was of more prognostic and therapeutic importance than the presenting skin or bone lesion. Eliminating duplications therefore in 20–25 per cent of the total number thorough study revealed that the therapeutic problem was one of cardiovascular visceral or neurosyphilis and that the benign late lesion was, from the standpoint of treatment, merely incidental. Patients in whom such complications exist should be managed in the light of the more serious involvement and in accordance with the principles set forth in the appropriate chapters.

The use of routine spinal puncture is as essential in benign late syphilis as in any other stage of the infection. In this series of patients the incidence of abnormal fluids (in 137 patients tested) was 13.8 per cent. Not all of the patients with clinical evidence of neurosyphilis had abnormal fluids and some of the latter were neurologically asymptomatic. The actual incidence of neurosyphilis clinical or asymptomatic in patients with benign late syphilis is about 15 per cent considerably lower than in patients with other types of late syphilis. This suggests as the Vienna school has for many years insisted and as has been shown in this country by Shaw that the allergic tendency offers some degree of protection to the neuraxis.*

*This does not mean, however that the routine examination of the spinal fluid in patients with benign late syphilis can be omitted.

Where the special lesions of cardiovascular visceral or neurosyphilis do not complicate the treatment problem, we have adhered in general to the same outline of treatment as that suggested for late latent syphilis (Chapter XVI) The important problem is to investigate the probability of clinical progression or relapse in relation to the amount and character of treatment.

Benign late syphilis in relation to earlier treatment —Each patient was questioned carefully as to treatment if any received prior to the appearance of the benign late lesion whether at the time of acquiring the infection or later The data are summarized in Table 52. Eighty-eight

TABLE 52

PREVIOUS ANTISYPHILITIC TREATMENT RECEIVED BY PATIENTS WITH BENIGN LATE SYPHILIS

Type of Late Syphilis	Total patients	Previous treatment			
		None	Inadequate		Adequate
			No arsphenamine	Some arsphenamine	
Osseous	100	85	4	11	0
Mucocutaneous	100	92	2	6	0
Total	200	177	6	17	

Only 4 of these received as much as 12 injections of an arsphenamine.

per cent had received no previous treatment of any kind only 8.5 per cent had ever been treated with any arsphenamine product and only 2 per cent had had as many as 12 injections of an arsphenamine. Like many other late manifestations of syphilis, then benign late lesions seem to be preventable by the adequate treatment of early syphilis.

The immediate therapeutic response of benign late syphilis —Therapeutic shock (the Jarisch-Herxheimer reaction) is of no importance in late mucocutaneous syphilides (excepting gumma of the larynx) In patients with osseous lesions the first injection of an arsenical drug is often followed within a few hours by an intense exacerbation of pain, lasting 12–24 hours. In most instances this exacerbation is in turn followed by prompt relief from all pain the patient is symptom free, perhaps for the first time in months. This is the usual course of events when the lesion is periosteal only if the whole bony structure is involved, disappearance of symptoms may be much more gradual requiring days or even weeks. In the series of 100 patients with bone lesions studied by Wasserman and Goodman, symptomatic relief followed the institution of treatment immediately in 73 and was delayed in 13 (no data were available in 14 instances)

Objectively there is rapid healing in skin lesions, even the largest

cicatrising within 6–8 weeks.* Little or no objective change takes place in proliferative osseous lesions, deformity if present is usually due to the deposition of new bone which treatment will not remove. Rarely (in 7 of the 100 patients in this series) surgical intervention for the removal of sequestra or for skin grafting of huge secondarily infected ulcerating skin lesions which overlie diseased bone † may be necessary before healing is complete. From the x-ray standpoint, improvement or its lack depends on the type of bony involvement. In most instances, the lesion is proliferative with new bone formation in these there is little or no change in the x ray picture even over a period of years. In a small proportion of cases, the bone lesion is destructive in them treatment leads to the deposition of new and healthy looking bone in the diseased area.

Skin lesions leave scars on healing, which are ineradicable. For a few months or even a year or more they may be deeply pigmented but in most instances pigmentation and discoloration gradually fade leaving partial depigmentation and atrophy

Serologic response in benign late syphilis —Seroresistance is the rule in benign late syphilis the serologic tests are irreversibly positive in more than two-thirds of the cases (Table 53) This phenomenon is twice as common as in late latent syphilis In our series of patients there is no

TABLE 53

SEROLOGIC RESPONSES IN PATIENTS WITH BENIGN LATE SYPHILIS

	Total cases	Serologic response in patients who received 3 or more courses of arsphenamine and heavy metal	
		Fast	Reversed
Osseous	54	37	17
Mucocutaneous	69	47	22
Total	123	84 (69%)	39 (31%)

direct relationship between seroresistance and total amount of treatment administered permanent reversal is secured no more frequently after 6 or more courses of treatment (of an arsphenamine with heavy metal) than after a less amount. Although the table indicates that seroresistance

* Antisyphilitic treatment has no effect on leukoplakia buccalis, the precancerous lesion so frequently associated with syphilis. This must be treated by the removal of all irritating factors (dental prophylaxis, prohibition of the use of tobacco, etc.) and by electrodesiccation or radiation.

† Surgical operations on previously untreated gummatous lesions of skin or mucosae may be productive of disastrous results in the form of spread of the gummatous inflammation. Also plastic operations on the scars of old gummatous lesions about the soft palate or posterior pharynx should be avoided, even though the patient has been thoroughly treated beforehand. Rapidly destructive gummatous lesions may reappear and spread in spite of treatment.

is as common in late cutaneous as in late osseous syphilis, it is actually slightly less frequent unless there is associated with the cutaneous lesion involvement of some other structure particularly the bones. At any rate, in benign late as in other forms of late syphilis the criterion of seroreversal is of little value as evidence of "arrest" or "cure," or as a measuring standard for optimum length of treatment.

The higher incidence of seroresistance in benign late as compared with late latent syphilis has often been used as an argument for the hypothesis that the phenomenon of persistently positive serologic tests depends on the persistence of active lesions or of foci of organisms and is of grave prognostic significance. We have already shown that, measured in terms of ultimate clinical outcome, this is not true of late latent syphilis (Chapter XVI) The point is re-examined for benign late syphilis in Table 54

TABLE 54

THE RELATIONSHIP OF SERORESISTANCE TO CLINICAL PROGRESSION OR RELAPSE IN BENIGN LATE SYPHILIS

(Limited to patients receiving 3 or more courses of treatment)

Type of serologic response	Total patients	Incidence of clinical progression or relapse	
		Present	Absent
Fast	91	9 (9 8%)	82
Reversed	49	6 (12.2%)	43

including only patients who received 3 or more courses of treatment. Instead of occurring much more frequently in seroresistant patients, relapse or progression is actually slightly more common in patients whose serologic tests have reversed to negative under treatment. As a matter of fact, the numbers involved are small and it is probable that the difference between the two groups, studied on a larger scale, is insignificant. At any rate, seroresistance conveys no gloomier prognostic outlook in benign late than in latent syphilis and seroreversal under prolonged treatment is no guarantee against subsequent relapse.

The ultimate clinical outcome in benign late syphilis —As in other types of late syphilis, the effect of treatment is much better measured by clinical than by serologic standards. If the patient s lesions heal, and if he remains well over an indefinite period of time, with no evidence of clinical progression or relapse of syphilitic lesions, the outcome is satisfactory regardless of whether seroreversal is or is not secured. In any case and regardless of serologic outcome, it is better for both physician and patient to think in terms of arrest rather than of cure.

Relapse or progression (the former more frequently than the latter) occurs more than three times as frequently in benign late as in late latent syphilis (disregarding the total amount of treatment, 16.4 per cent as

compared with 4 9 per cent) There is more readily apparent also a direct relationship between relapse and total amount of treatment in benign late syphilis than in latent syphilis where relatively little treatment seems to prevent relapse as effectively as a great deal This relationship in benign late syphilis is shown in its simplest form in Table 55 When the patient

TABLE 55
RELAPSE OR PROGRESSION IN BENIGN LATE SYPHILIS ITS RELATION TO AMOUNT OF TREATMENT

Amount of treatment (arsphenamine and heavy metal)	Total patients	Number of patients in whom progression or relapse was	
		Present	Absent
1 course or less	40	17 (42.5%)	23
2–3 courses	74	9 (12.1%)	65
4 courses or more	81	6 (7 4%)	75

receives one course or less of an arsphenamine plus a heavy metal the probability of subsequent progression or relapse is nearly six times as great as if he receives four courses or more. Indeed under the former conditions, further progress may be expected in at least four patients of every ten. No examples of relapse were observed in 14 patients who received 7 or more courses of combined arsphenamine and heavy metal therapy These data are subject to future modification on two grounds first, that the number of cases studied is relatively small and second that the patients in this group in whom relapse or progression have not occurred have been under observation for an average period of only 4 5 years (15 of the total 163 for 10 years or longer) That some at least of the patients now regarded as well may subsequently relapse is suggested by the fact that the average time interval between the last treatment and the appearance of fresh lesions, when these occurred was 4 5 years. Eighty per cent of all relapses occurred within 6 years after the cessation of treatment, but in three instances the interval was 10 years or longer The results presented in Table 55 seem therefore, to represent the maximum of good results obtainable.

The character of relapse or progression is of extreme interest (Table 56) This is practically always of the same type as the original lesion. Thus of 19 relapsing patients with osseous syphilis the relapse involved the appearance of lesions in previously uninvolved bones in 9 Of 13 patients whose original lesion involved the skin new late mucocutaneous lesions appeared in six. The allergic tendency is not abolished by treatment 65 per cent of all relapses were of the allergic inflammatory type involving skin mucosae bones or eye. In 3 of 6 patients the subsequent central

TABLE 58

CHARACTER OF PROGRESSION OR RELAPSE IN BENIGN LATE SYPHILIS

Type of original lesion	Total patients relapsing	Character of Relapse					
		Allergic inflammatory			Cardio-vascular	Central nervous system	Visceral
		Bone	Muco-cuta-neous	Ocular			
Osseous	19	9	2	1	2	4	1
Mucocutaneous	13	2	6	1	2	2	—
Total	32	11	8	2	4	6	1

Sixty-five per cent of all relapses were of the allergic inflammatory type.

nervous system involvement represented progression of a lesion already present before any treatment was started (paresis in all) in two the appearance of fresh lesions (cranial nerve palsies) not present before treatment and in one, the development of abnormalities in a previously normal spinal fluid In all of the 4 patients with cardiovascular progression, the lesion had been present before treatment, but grew worse in spite of it. The one example of visceral relapse is accounted for by a patient who developed *cirrhosis of the liver of questionable etiology*

Fourteen of the 200 patients in this series are dead of whom 8 died certainly or probably of syphilis (cardiovascular or neurosyphilis in all) and 6 of unrelated causes.

The character of treatment, i.e. whether continuous or intermittent, appears as in late latent syphilis, to play little rôle in the ultimate outcome. There is no evidence that rest periods, if not too prolonged do any harm.

The optimum amount of treatment in benign late syphilis — It seems clear from this study that the average patient with benign late syphilis requires more treatment in terms of an arsenical drug of heavy metal and of total duration than the average patient with late latent syphilis. For the latter we have suggested on the basis of the studies of the C C G and of Diecker a treatment plan including approximately 24 injections of an arsenical and 30 of bismuth over an average time period of 1 year The results of Wasserman and Goodman s study of benign late syphilis indicate that with only this amount of treatment, relapse may occur in at least 10 per cent of such patients treated and that for maximum protection against relapse a total of at least 7 courses each of an arsenical and a heavy metal is essential. Our personal preference is for continuous treatment not so much because it is necessitated as in early syphilis by urgent considerations, but rather because it is easier to hold the average patient to his task if he is required to keep at it regularly without intermissions. Continuous treatment involves, of course the alternating use

of an arsenical and a heavy metal as suggested in Table 57 The total duration of the suggested treatment, given continuously is a little greater than 2 years. Any of the arsphenamine products or mapharsen may if desired be substituted for neoarsphenamine during part or all of the course. It is suggested that the first four courses of neoarsphenamine be of 8 doses each the last three of 6 doses each that the first course of bismuth be of 8 injections, subsequent ones of 10 injections each. These

TABLE 57

SUGGESTED OUTLINE OF TREATMENT FOR UNCOMPLICATED BENIGN LATE SYPHILIS

Weeks	Drug	Remarks
1–7	8 doses neoarsphenamine, 0 45–0.6 gm	Test spinal fluid before starting treatment or as soon as possible thereafter If positive, modify this plan.
8–15	8 doses bismuth subsalicylate, 0.2 gm.	Neoarsphenamine appears to be as satisfactory as any other arsphenamine product. Mapharsen may likewise be used preferably in maximum dosage (0.06 gm.)
16–23	8 doses neoarsphenamine	Use potassium iodide for first 4 months, and during bismuth courses thereafter
24–33	10 doses bismuth	
34–41	8 doses neoarsphenamine	
42–51	10 doses bismuth	Do serologic tests from time to time, but disregard serologic progress. Do not stop if serology becomes negative.
52–59	8 doses neoarsphenamine	
60–69	10 doses bismuth	
70–75	6 doses neoarsphenamine	
76–85	10 doses bismuth	
86–91	6 doses neoarsphenamine	
92–101	10 doses bismuth	
102–107	6 doses neoarsphenamine	
108–117	10 doses bismuth	
Thereafter—	None unless necessitated by clinical progression or relapse	Test serologically (quantitative titre) every 6 months. Periodic physical examination every 12–24 months.

suggestions are subject to individual variation but the idea in mind is that, as compared with early syphilis relatively less arsenical and relatively more heavy metal be administered particularly in the latter part of treatment.

Post treatment follow up —As with all other types of syphilitic infection the patient should be kept under observation indefinitely The serologic tests may be repeated at intervals of 3 months for the first year and semi-yearly thereafter If they are persistently positive such tests are of little value unless quantitatively titered and there is no indication for resuming treatment on serologic grounds unless there is a confirmed significant increase in serologic titre (beyond the limits of laboratory variation) In our experience such an increase is uncommon the serologic tests usually hold to a more or less constant level of positivity or even

tend toward spontaneous reversal (Fig. 39) The spinal fluid, if originally negative, need never be retested (Chapter XXI)

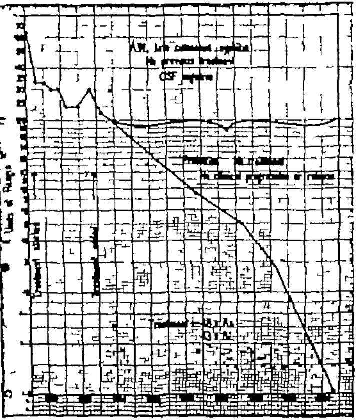


FIG. 39 —Illustrating the spontaneous disappearance of reagin from the blood during 7 years of post-treatment observation and the usefulness of quantitative serologic testing under these conditions.

Repeated physical surveys with special emphasis on examination of the heart and aorta, should be carried out every year or two as long as the patient lives.

Ununited fractures —This uncommon complication of syphilis is discussed in detail in Chapter XXV

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CHAPTER XVIII

THE TREATMENT OF CARDIOVASCULAR SYPHILIS

WE MAKE no apology for including in a chapter on the treatment of cardiovascular syphilis some details as to the correlation of the clinical and pathologic features of this condition and some comments on its early diagnosis. Excepting only neurosyphilis and perhaps even exceeding this cardiovascular involvement is the most frequent basic cause of death from acquired syphilis. Efforts to deal with it as a cause of incapacity and death will be furthered by the ability to recognize its existence in the stage of uncomplicated aortitis, before the development of irreparable anatomic damage in the form of valvular incompetency or saccular dilatation. Finally the whole subject is of especial importance because of the scepticism which still prevails as to the desirability of antisyphilitic treatment and of *the benefits obtainable from* it *in the more advanced forms* of the condition.

The frequency of cardiovascular syphilis.—There are wide variations between clinical and pathologic estimates of the incidence of involvement of the cardiovascular apparatus in patients with syphilis. From the clinical standpoint, Bruusgaard's figures and those from our own clinic are in essential agreement. Bruusgaard had the exceptional opportunity of reviewing the status of 473 patients who had received no treatment for early syphilis at long intervals after infection, ranging between 10 and 40 years and averaging about 20 years. Of these patients approximately 10 per cent developed definite clinical evidence of cardiovascular damage. In our own material *Turner's statistical survey of the admission diagnosis* of more than 6 000 patients with untreated late syphilis showed also that 10 per cent were suffering from cardiovascular syphilis (5.3 per cent uncomplicated aortitis 1.2 per cent aortic aneurysm 2 7 per cent aortic insufficiency 0 7 per cent other scattering diagnoses)

These data are in striking contrast to the information furnished from necropsy studies by such observers as Langer Warthin and Nickel. On *the basis of very large material, these investigators find that from* 70 to 90 per cent of all patients with late syphilis *which is diagnosable post mortem* show pathologic evidence of cardiovascular damage, most commonly syphilitic aortitis. The discrepancy between clinical and pathologic estimates is due first to the fact that in many instances the *pathologic* diagnosis is based on the presence of lesions in the aortic wall so insignificant as to be below the threshold of physiologic disturbance and hence of clinical recognition and second that these studies do not relate the observed necropsy incidence of cardiovascular syphilis to the clinical and serologic evidence of syphilis in the population from which the patients are drawn.

In spite of this, the pathologic evidence is of clinical significance in that

it indicates that some degree of syphilitic involvement of the aortic wall is a frequent accompaniment of long-standing untreated syphilitic infection. It should prompt the clinician to painstaking and repeated investigation of the cardiovascular apparatus of every patient with late syphilis.

From the more general point of view the studies of White's group and Maher and his collaborators show that cardiovascular syphilis is responsible for from 5–10 per cent of all clinically recognizable cardiovascular disease.

The classification of cardiovascular syphilis.—Much of the confusion which has beclouded the treatment problems of cardiovascular syphilis depends on the tendency to a loose use of terminology to a

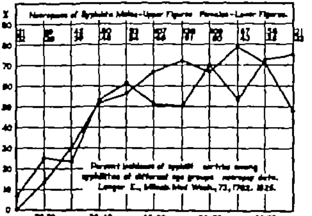


FIG. 40

grouping of all cases as "cardiovascular syphilis" or as "syphilitic aortitis." Too much has been written about the diagnosis and treatment of cardiovascular syphilis without the attempt more sharply to delineate clinical syndromes within this large disease group. It is important to remember that the location and extent of the lesion may produce a variety of clinical pictures. In the light of our present knowledge, these may be separated into six more or less clearly defined groups. First, there may occur pathologic involvement of the aortic wall so slight as to produce no symptoms and no physical signs. Second, a more advanced stage represents diffuse and primarily supravalvular involvement of the aorta, resulting in the production of uncomplicated syphilitic aortitis with or without diffuse dilatation. When the latter is present the condition has been designated by some observers as fusiform aneurysm, though we regard this terminology as unfortunate as tending to identify this condition with one of more serious prognostic import. Third, if the lesion has produced a more or less localized destruction of elastic fibres anywhere in the aortic wall (usually in the ascending portion of the aorta), a saccular

CHAPTER XVIII

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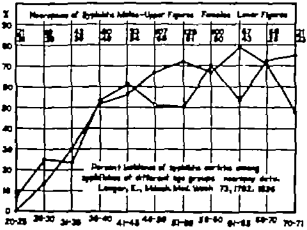


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dilatation may occur It is for this condition that we prefer to reserve the use of the term 'aneurysm. Fourth if the lesion by extension downward encroaches upon the insertion of the aortic leaflets subsequent distortion and valvular incompetency appear with immediate mechanical effects apparent in the heart and peripheral vessels. Fifth there is a small group of cases in which progressive heart failure is consequent to chronic myocardial ischaemia produced by stenosing lesions of the coronary ostia without accompanying valvular disease. Sixth and last and presenting a similar clinical picture is the equally small group of patients with true syphilitic myocarditis.

In considering methods and results of treatment it is essential clearly to identify the type of cardiovascular syphilis under discussion. The prognosis is vastly better and the choice of treatment procedures different in patients with uncomplicated aortitis than in patients in whom aneurysmal sacculation aortic insufficiency or pronounced myocardial damage (whether on an inflammatory or mechanical basis) have already appeared.

The clinical recognition of uncomplicated aortitis —The problem of clinical recognition of the existence of cardiovascular syphilis before irreparable anatomic damage has been done justifies the inclusion in the consideration of treatment of a brief discussion of the diagnosis of uncomplicated syphilitic aortitis. There is widely prevalent a feeling that this diagnosis is difficult or impossible to make because of the similarity of symptoms and physical signs caused by this lesion and by such other conditions as aortic atherosclerosis or essential hypertension. From a comparison of clinical and necropsy observations, Moore Danglade, and Reisinger listed seven clinical criteria, the presence of any three of which they thought could be considered as strong evidence for the diagnosis of uncomplicated syphilitic aortitis.

Further experience and studies still in progress however indicate the necessity for revision of those criteria with particular reference to more critical examination of roentgenologic studies of "aortic width and to the importance of careful evaluation of symptoms. At present it does not seem possible to establish a tenable clinical diagnosis of uncomplicated aortitis in many patients with late syphilis despite the fact that subsequent necropsy reveals the lesion to have been present. On the other hand there are clinical criteria the proper evaluation of which does frequently permit the diagnosis which can later be anatomically verified. These are

1 Roentgenologic demonstration of dilatation of the first portion of the aorta. This should be by fluoroscopy the use of the oblique positions or roentgenkymography It cannot rest on the routine postero-anterior teleroentgenogram and the Vaquez-Bordet measurements of "aortic width ' unless distortion be extreme.

2. Heart failure or lowered cardiac reserve in the absence of hyper tension or valvular disease Failure may be either congestive or anginal paroxysmal dyspnea is probably an anginal equivalent and lowered cardiac reserve usually first reveals itself by dyspnea on exertion.

3 Localized substernal pain (to be differentiated from anginal pain)

which characteristically is dull, aching, relatively constant and is neither influenced by exertion nor referred down the arms.

4. Characteristic changes in the second aortic sound. Accentuation in contrast to the other heart sounds is the rule and especially an alteration in quality best described as tympanitic bell-like, tambour, i.e. approaching a pure musical note.

Of these definite roentgenologic evidence is the most diagnostic. The evaluation of symptoms calls for much experience when they are minor, but when they are outspoken leads readily to the diagnosis Finally it must be emphasized that with the large variations in intensity and quality of the second aortic sound which normally occur significance should be attached only to the most outspoken changes

In the original study by Moore Danglade, and Reisinger covering the period 1910–1930 the clinical diagnosis of uncomplicated syphilitic aortitis later confirmed by necropsy was correctly made in only 6.2 per cent of a group of medical (as contrasted to surgical) patients A restudy of the question during the period 1931–1940 shows that with attention to the criteria enumerated, the incidence of correct clinical diagnoses in a comparable series of patients in the Johns Hopkins Hospital has risen to 26.3 per cent (Mattman) We are convinced, therefore, that the correct diagnosis of uncomplicated aortitis will increase if the physician remembers that aortitis is a frequent pathologic finding in late syphilis if he pays particular attention in history taking to questions calculated to bring out the presence of lowered cardiac reserve, paroxysmal dyspnea and substernal pain if he searches for the common physical signs and above all, if he uses proper roentgenologic examination as a routine in patients who have syphilis ten or more years.

The prognosis of untreated cardiovascular syphilis —It is pertinent to enquire what may be expected to happen to a patient with cardiovascular syphilis provided he receives no treatment. Only with a knowledge of the natural evolution of any disease process if untreated can one be sure that any type of treatment is successful in ameliorating the condition. Schlesinger has emphasized the fact that in uncomplicated syphilitic aortitis the ultimate prognosis may be good in spite of the fact that the patient receives no treatment whatever He bases his contention on four facts, to all of which we subscribe —first, on the discrepancy between the relative infrequency of clinical evidence of cardiovascular damage and its relative great frequency at necropsy second, on the fact that the incidence of syphilitic aortitis observed post mortem steadily increases with increased age and that it is highest in the decades above 60 third, on the point that while aortitis is common at necropsy of patients with late syphilis, it is relatively infrequently the cause of death (among our own 105 patients diagnosed by the pathologist, only 24 died of causes in any way related to syphilis and of these only 10 died as a probable direct result of the aortitis in 81 of the group or 77 per cent, the final illness had no relation to syphilis or aortitis) and fourth, on the prolonged follow-up of patients with uncomplicated aortitis by various ob-

servers as for example Hubert who found among 137 cases still under observation the duration of life since the onset to be six and one-half years Forty-seven of his patients were completely free of symptoms in spite of the absence of all treatment and 44 of the total number were able to work.

The situation is quite different in patients who developed aortic insufficiency or aneurysm In the former group the average duration of life following the onset of symptoms in patients who are not treated is from 2 to 3 years and in patients with aortic aneurysm untreated from 1 to 3 years. *These statements are based on our own experience as well as on a* consensus gathered from the literature. In our own material the average duration of life dating from the onset of symptoms in untreated patients with aortic aneurysm was 19 months and in untreated patients with aortic regurgitation, 30 months. We can offer no definite figures as to the duration of life in patients with syphilitic involvement of the coronary ostia or the myocardium inasmuch as such cases are so few as to make statistical estimates unreliable The evidence is, however that either of these manifestations, particularly the latter tends to shorten life even more than the other lesions mentioned

We anticipate for a moment the results of treatment in the prolongation of life in patients with cardiovascular syphilis to include them in a brief tabular summary indicating the various common types of cardiovascular syphilis their approximate frequency in patients *with late syphilis* and their prognosis in terms of duration of life if untreated and if adequately treated.

TABLE 58

THE INCIDENCE AND PROGNOSIS OF VARIOUS TYPES OF CARDIOVASCULAR SYPHILIS

Clinical type of cardiovascular syphilis	Approximate percentage of patients with late syphilis affected	Prognosis in terms of probable average duration of life if	
		Untreated	Adequately treated
Uncomplicated aortitis clinically unrecognizable	70–90	Good—many years, no accurate data	Excellent—life probably not shortened
Uncomplicated aortitis, recognizable on basis of symptoms and signs	5–10	5–10 years	10–20 years or better
Aortitis with saccular aneurysm	1–2	1–2 years	5–10 years
Aortitis with aortic regurgitation	2–3	2–3 years	4–10 years
Myocarditis Coronary ostial stenosis	0 2–0 5	No accurate data	No accurate data

The prophylaxis of cardiovascular syphilis by the adequate treatment of early syphilis —It is much easier to prevent the development of cardiovascular syphilis than it is to treat it after it has appeared. There has been debate however over the question as to whether the adoption of modern methods for the treatment of early syphilis has increased the incidence of cardiovascular syphilis. Some observers believe that the widespread use of the arsphenamine products has resulted in an increase in the incidence of syphilitic aortitis in recent years. The studies of Kemp and Cochems Rosahn, and Padget clearly show this to be quite untrue. These authors approaching the problem from different points of view each show that the chance for a patient later to develop cardiovascular involvement diminishes directly with the amount of treatment given by a continuous system for early syphilis and that the risk practically disappears after an amount of continuous treatment (about 9 doses of an

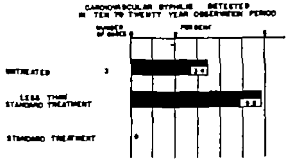


FIG. 41 —Probability of developing cardiovascular syphilis in treated and untreated early syphilis (from Vonderlehr and Usilton)

arsphenamine) which is wholly inadequate for the prophylaxis of neurosyphilis.

Equally satisfactory results in the prevention of cardiovascular syphilis may be obtained by the treatment of latent syphilis at any interval after infection. The C C G has studied the outcome of treatment in 1,936 patients with latent syphilis in none of whom could the diagnosis of cardiovascular syphilis be made before treatment. The condition was later observed to develop in only 31 patients following treatment. Since reasoning by analogy from pathologic evidence subclinical lesions must have been present in the aortae of many of these patients this result can be interpreted to mean that treatment has prevented its further progress and the development of symptoms or physical signs. It is fair to assume further that if this result can be accomplished in late latent syphilis it may also be achieved in other forms of late syphilis without apparent cardiovascular involvement. The importance of these points lies in the fact that every patient with outspoken cardiovascular involvement passes through a preliminary stage of clinical latency during which his infection is nevertheless recognizable and if recognized may be treated with reasonable assurance that cardiovascular syphilis will not develop

The ideal method of treatment of cardiovascular syphilis, therefore, lies

in the hands of the physician who sees the syphilitic patient before the development of clinical evidence of cardiovascular involvement and who applies modern therapy at a time when although the aortic wall may already have been invaded, tissue involvement in this area is at a minimum

The aims of treatment in cardiovascular syphilis.—The aim of treatment in cardiovascular syphilis is not the radical cure of the syphilitic infection, nor even the restitution of the damaged structures to anatomic integrity These aims are obviously impossible. Radical 'cure' is as improbable as in other forms of late syphilis. One cannot replace dead elastic tissue in the aortic wall nor remake distorted valve leaflets. The best that one can hope for is to bring about healing of the active inflammatory process and its replacement by connective tissue, to prevent the development *of fresh inflammatory lesions in the involved structures* and to compensate so far as possible for the mechanical damage done to the cardiovascular apparatus From the standpoint of the patient, this is tantamount to saying that the two primary aims of treatment are the relief of distressing symptoms and the prolongation of life past the average duration to be expected had no treatment been given These aims can often be accomplished by a judicious combination of general medical care and of antisyphilitic treatment. It is no longer justifiable to withhold specific treatment from patients with cardiovascular syphilis even when the situation seems hopeless. Treatment can be adjusted so as to do no harm and almost miraculous recoveries may sometimes be secured.

The principles of treatment of cardiovascular syphilis.—The essentials on which the formulation of a treatment scheme for patients with cardiovascular syphilis are based may be summarized as follows —first a clinical evaluation of the location and extent of the anatomic damage and its present and potential physiologic consequences second permanent limitation of physical activity to a degree dictated by the extent of the involvement, and initiated in all but the least serious with a long period of full bed rest in hospital third general medical care with especial reference to the proper use of digitalis the mercurial diuretics and morphine fourth special treatment methods such as the wiring of aneurysms etc. fifth specific treatment.

In planning specific treatment, five cardinal principles must be kept in mind *all of which are based on the fundamental fact that any scheme of* treatment must be one calculated to do no harm. The first essential is the absolute avoidance of a grave immediate treatment reaction particularly associated with cardiovascular syphilis. It has long been known that the arsphenamines, and especially old arsphenamine itself when given to a patient with cardiovascular syphilis, may produce during or immediately *after treatment* a syncopal reaction with sudden circulatory failure the patient dying within a few minutes. Such reactions, only too common in the early days following the introduction of arsphenamine, are probably due to the sudden production of ventricular fibrillation (Chapter VII) This phenomenon is more common after arsphenamine than after any *other of the allied products* and the disastrous outcome of immediate death during treatment is in large part responsible for the disrepute into

which all treatment efforts in cardiovascular syphilis fell for a period of several years. The reaction may be in part dependent on the bulk of fluid injected, and in part on the size of the dose administered. It may be largely avoided by the use of the less toxic arsenical drugs, neoarsphenamine silver arsphenamine mapharsen or bismarsen all of which are soluble in small amounts of water and all of which for caution's sake should be given in very small doses. Old arsphenamine (606) should never be employed in any dosage in patients with aortic regurgitation or aortic aneurysm.

The second principle of treatment is that one must attempt to avoid not only this disastrous reaction but also all treatment reactions. It is undesirable to place any added strain on an already over-burdened myocardium and even so mild a post treatment upset as a few hours of nausea and vomiting should if possible, be entirely eliminated This too may be accomplished by the use of small doses of the least toxic arsenical drugs. In the absence of renal damage, bismuth is without deleterious effect on the cardiovascular apparatus and may be employed in average therapeutic dosage.

The third danger to be guarded against is the production of therapeutic shock, the so-called Jarisch-Herxheimer reaction This flare-up or intensification of a syphilitic lesion a few hours after the first injection of an arsphenamine product becomes of paramount importance when the lesion may be located at the mouth of a coronary artery in the wall of an aneurysm or in the myocardium. In these locations the associated sudden local edema may result in coronary occlusion, aneurysmal rupture or ventricular fibrillation, in each case with an immediately fatal outcome This reaction may be prevented by inaugurating treatment with drugs which are not so rapidly treponemicidal and which produce healing and resolution of lesions more slowly than the arsphenamines. This can best be accomplished with bismuth and the iodides, which should be employed for a long enough period of time before the inception of arsenical therapy to be reasonably sure of the probability of some healing of the syphilitic inflammatory tissue and its replacement by connective tissue elements. Reasoning by analogy from more easily visible lesions the approximate length of time necessary to accomplish this in cardiovascular syphilis is from 8 to 12 weeks. Even when this period of preparatory treatment is ended the danger of therapeutic shock is not yet entirely passed, so that treatment with the arsenical drugs should be started with extremely small doses for example, 0 05 to 0 1 gm. of neoarsphenamine or 0 010 gm of mapharsen.

The therapeutic paradox is a fourth element of danger Attention was drawn to this phenomenon some years ago by Wile, who pointed out that in certain patients with cardiovascular syphilis and with previously adequate cardiac compensation treatment resulted in an initial period of symptomatic improvement which was followed by the sudden appearance of congestive heart failure. This is probably due to the too rapid healing of syphilitic inflammatory tissue which is replaced by contractile scar with the result that the lesion is pathologically better but the patient is

functionally worse than he was before treatment began Fortunately this development is uncommon and largely may be obviated by the precautions outlined above.

The next risk which must be considered is that of giving too intensive treatment of any type to a patient who has previously had, or is in the midst of an attack of congestive heart failure When decompensation is actually present on admission the first essential is to treat the patient by the usual methods for dealing with congestive heart failure before attempting more than the absolute minimum of antisyphilitic treatment. In the presence of failure, our practice is to limit specific treatment to usual (6 gms. daily) doses of potassium iodide by mouth and if edema be troublesome and no contra-indications exist daily or triweekly injections of a usual dose of one of the mercurial diuretics not only for its diuretic but also and quite incidentally for its antisyphilitic effect. Prolonged bed rest slow convalescence and graduated exercise are all employed in the effort to build up some degree of cardiac reserve before the use of even moderately large doses of bismuth or of any dosage of an arsenical

The fifth principle of treatment is that it should be prolonged to an absolute minimum of two years and that, so far as possible it should be continuous.

The details of treatment —In patients with *uncomplicated syphilitic aortitis* without aortic regurgitation or aneurysm some of the above precautions are unnecessary It is always wise because of the incalculable factor of possible coronary involvement, to begin treatment with a preparatory course of bismuth and potassium iodide for from 2 to 3 months before treatment with an arsenical drug is attempted. In the absence of aortic insufficiency aneurysm or congestive heart failure however all the arsenical drugs even old arsphenamine itself are fairly well tolerated and the dosage may be much larger than when any of these complications are present. It is better to start with a small dose, for example 0 1 gm. of neoarsphenamine, or 0 010 gm mapharsen and to increase this dosage cautiously to the usual maximum The two drugs are probably equally effective in comparable dosage the relative infrequency of immediate "minor" treatment reactions following the use of mapharsen particularly recommends it for use here It is better to use an arsenical drug and a heavy metal in alternation rather than simultaneously in order to ease the strain of antisyphilitic treatment on the patient. We believe on clinical grounds that patients do better on continuous treatment without rest periods than on intermittent treatment with interpolated intervals. Courses of both arsenical and heavy metal drugs tend to be long i.e. 10 to 12 weekly injections of each. Treatment is prolonged regardless of serologic progress for a period of at least 2 years. In most patients including those who have progressed satisfactorily we believe it to be wise to keep the patient under the most rigid post treatment observation for the balance of his lifetime and occasionally perhaps once a year to administer a course of a heavy metal to be followed by a course of an arsenical drug.

In patients who have already developed *aortic insufficiency* or *aneurysm*,

treatment must be much less intensive. The manner of its start depends largely on whether or not compensation has already been lost If so active treatment is postponed until it can be regained The usual preparatory course of treatment consists of small doses of an insoluble bismuth salt, for example, 0 1 gram every 4 or 5 days to be increased if the patient tolerates it without difficulty to 0.2 gram once a week. At the same time, potassium iodide is given in large doses up to 12 grams a day divided into three doses This is continued for 10 to 12 weeks before any arsenical drug is used In many patients a satisfactory degree of cardiac reserve cannot be obtained and in them treatment with the arsenicals is permanently avoided. If however the patient has adequate compensation or recovers it by the end of the preparatory course to an extent which enables him to be ambulant without edema or marked exertional dyspnea, arsenical treatment is started with small doses of neoarsphenamine or mapharsen intravenously (0 05–0 1 gm of the former 0 010 gm of the latter) or bismarsen intramuscularly (0 1 gm) at weekly intervals A maximum dosage of 0 3 gm. of neoarsphenamine 0 030 gm mapharsen, or 0.2 gm. bismarsen is never exceeded. As with uncomplicated aortitis courses of both heavy metal and arsenical are long (10–12 weeks) and treatment is prolonged for a minimum period of two years.

These details may be modified to the point of complete abandonment by such factors as the patient s age his poor general physical condition or such complications as hypertensive cardiorenal disease

PRINCIPLES OF TREATMENT OF CARDIOVASCULAR SYPHILIS

Treat the patient in such a way as to do no harm.

General medical care

1 Rest.

2 Restriction of physical activity

3. Digitalis when needed

4. Nitroglycerin and theobromine derivatives for pain.

Specific Treatment

1 Avoid immediate grave treatment reactions—ventricular fibrillation. Do not use arsphenamine (606) in any dosage.

2. Avoid even minor treatment reactions if possible. Use mapharsen. neoarsphenamine or bismarsen in small doses.

3. Avoid therapeutic shock—the Herxheimer reaction. Begin treatment with bismuth and the iodides.

4. Avoid the therapeutic paradox. Continue preparatory heavy metal treatment for 8–12 weeks before attempting arsenicals.

5. M ke treatment prolonged—minimum 2 years—and continuous.

FIG. 42

Digitalis in the treatment of cardiovascular syphilis.—In the absence of symptoms of lowered cardiac reserve digitalis is not indicated. In ambulant patients who are troubled with moderate exertional dyspnea but who do not have other symptoms of congestive failure the powdered leaf in a "tonic" dosage of 0 1 gm. daily is often productive of much relief When actual congestive failure has occurred the patient should be placed at complete bed rest at once, and digitalized fully as promptly as possible. In many patients with low cardiac reserve the drug may be given in maintenance dosage (usually 0 1 gm. of the powdered leaf daily) over indefinite periods of time and often continuously (Christian) It must be remembered that patients with cardiovascular syphilis especially Negroes are sometimes more refractory to digitalis than those with heart failure due to other causes and that even huge doses may fail to produce desired effects.

The results of treatment in patients with uncomplicated syphilitic aortitis.—Using the earlier criteria for the diagnosis Moore and Metildi studied the outcome in relation to treatment in 115 patients in whom the clinical diagnosis of uncomplicated syphilitic aortitis had been made. Unfortunately we do not have available in this group as in the groups of patients with aortic insufficiency and aneurysm to be mentioned presently an adequate number of untreated control patients so that it is impossible to discuss with authority the probable prolongation of life by treatment. However our living well-treated patients were followed for an average period of 8 years Results are expressed in terms first of mortality rate and second of the development, in patients still living as well as those dead of such definite graver forms of cardiovascular syphilis as saccular aneurysm and aortic regurgitation.

This information is shown in Table 59 for two groups of patients, i.e.

Table 59

Effect of Treatment on the Outcome of Uncomplicated Syphilitic Aortitis (Moore and Metildi)

Amount of treatment	Total patients	Mortality rate, all causes, per cent	Incidence of development of graver forms of cardiovascular syphilis (aneurysm aortic regurgitation, death from congestive heart failure) per cent
None or inadequate (less than 12 doses of an arsenical)	45	42	31
Adequate (more than 12 doses of an arsenical)	70	14	19

those who received no or inadequate treatment (less than 12 injections of an arsenical product with interim heavy metal) and those treated adequately (more than 12 injections of an arsphenamine and in the majority

of instances more than a year of continuous treatment) The mortality rate is based on all patients dead from any cause whether or not related to syphilitic aortitis. In spite of this strict interpretation of mortality there is a clear cut difference in the outcome 42 per cent of those inadequately treated are dead, and 31 per cent have developed aneurysm aortic insufficiency or have died as a result of congestive heart failure as compared with corresponding figures of 14 and 18 per cent for the adequately treated group

It is not surprising that aortic regurgitation may develop in spite of thoroughly adequate treatment (8 of 47 patients in the best treated group) In some instances it is probable that the development of valvular incompetency is actually hastened by treatment. With the healing effect of treatment, inflammatory tissue in a still competent valve may be replaced by scar with subsequent distortion and the production of mechanical insufficiency This may be a blessing in disguise rather than a disaster since, as Stokes puts it, a progressive disability has been exchanged for a static one.

Relief from symptoms especially pain and dyspnea, as a result of treatment is usually so prompt and complete in patients with uncomplicated aortitis as to leave some doubt of the correctness of diagnosis when it does not occur This is indicated in Table 60 which shows that symptomatic

TABLE 60

SYMPTOMATIC RELIEF IN UNCOMPLICATED AORTITIS

Treated patients with symptoms	Symptomatic relief obtained in	
	Patients	Per cent
75	63	84

relief was obtained in 84 per cent of treated patients. It is an unfortunate feature of symptomatic relief that the unintelligent patient is often persuaded that he is cured by a few weeks of treatment and fails to return. Unfortunately also relief often is not permanent, and symptoms tend to recur with long lapses in treatment.

As illustrative of the relatively favorable prognosis of uncomplicated aortitis, 86 of our 115 patients were still living at the time of report. Among those well treated (40 in number) the average duration of life, dating from the diagnosis of aortitis was 8 years and 57 per cent of this group were completely symptom free without progress in physical signs.

The results of treatment in aortic aneurysm and aortic regurgitation —The results of treatment in patients with aneurysm and aortic regurgitation can best be shown by a brief summary of the studies which were made with Dangiade and Reisinger and later extended with Padget, which were based on the follow-up of 53 patients with aortic aneurysm and 112 with aortic insufficiency Fifty three of these patients died in less than a year of observation and so are excluded from a consideration of the results of antisyphilitic treatment, since the time factor

alone made the administration of adequate treatment impossible In 1941, 3 of the patients originally reported on (in 1930) were still living (all adequately treated) and 2 have been lost from observation. The remaining 107 are now all dead affording a comparison of the duration of life in those inadequately treated as compared to those adequately treated (Fig 43) Among 36 patients with saccular aneurysm and 71 with aortic regurgitation the mean duration of life from onset of symptoms to death was approximately doubled by adequate treatment.

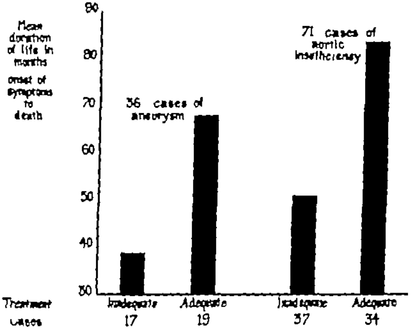


FIG. 43.—Duration of life in aneurysm and aortic insufficiency (adequate versus inadequate treatment)

The original study showed the prejudicial effect on the ultimate outcome of congestive heart failure occurring before treatment in patients with aneurysm and aortic insufficiency both in mortality rate and duration of life in those dead It is now apparent however that the patients belong in two groups those who die relatively shortly (a few months) after first developing symptoms and those in whom the course of the disease is naturally more prolonged even without the effects of antisyphilitic treatment. Among the former the development of congestive failure marks the onset of a rapidly progressive fatal illness the course of which is relatively uninfluenced by the usual remedial measures. Many of the latter however recover from a first attack of congestive failure to exhibit no discernible alteration in the subsequent course of the disease. It seems fair to say therefore that the presence or development of congestive failure is a grave complication which is to be feared but that if recovery of compensation occurs, the prognosis for the future is not seriously altered

As in patients with uncomplicated aortitis partial or complete symptomatic relief as a result of antisyphilitic treatment is usually obtainable in those with aneurysm or aortic insufficiency Information as to this point, contrasting untreated with well treated patients, is shown in Table 61. It must be emphasized that patients in both groups received approximately the same type of general medical care, including rest, restriction of activities and digitalis so that the 94 per cent symptomatic relief obtained in well treated patients as contrasted to the 24 per cent relief in those untreated is a direct reflection of the effect of antisyphilitic treatment. Improvement may be prompt but is often much slower than in uncomplicated aortitis, and likewise, discontinuance of treatment may result in a prompt exacerbation of symptoms. Persistence, patience and encouragement are essential.

TABLE 61

SYMPTOMATIC RELIEF IN PATIENTS WITH ANEURYSM OR AORTIC REGURGITATION

Amount of treatment	Total patients	Symptomatic relief obtained in	
		Patients	Per cent
None or very little	37	9	24
Adequate (more than one year)	31	29	94

As with uncomplicated aortitis, treatment proceeds regardless of serologic progress. Fixed positive serologic reactions in the blood in spite of treatment are found in more than half the patients.

The treatment of syphilitic myocarditis —The rare patient in whom the clinical diagnosis of syphilitic myocarditis can be made may be subjected to the same general type of management suggested for patients with aortic regurgitation or aneurysm complicated by congestive heart failure. Even more caution will be required in antisyphilitic treatment, however as congestive failure is harder to ameliorate by rest and digitalis when the myocardial lesion is on an inflammatory rather than a mechanical basis, and satisfactory cardiac reserve is less likely to be regained.

The treatment of coronary ostial stenosis —In the infrequent patient, stenosis of the coronary ostia, through the production of chronic myocardial ischaemia, leads to the development of congestive failure and a clinical picture which may be confused with that produced by syphilitic myocarditis. More commonly however the lesion produces no signs or symptoms discernible as such but in patients with aortic regurgitation the eventual outlook may depend largely on its presence or absence The constant possibility that this lesion may be present in any patient with cardiovascular syphilis (or for that matter any form of untreated late syphilis) urgently necessitates the institution of antisyphilitic treatment with a heavy metal never an arsenical. Otherwise treatment proceeds as in the other forms of cardiovascular syphilis.

Schematic outlines of treatment for cardiovascular syphilis — In order to summarize briefly the information provided in the preceding pages, we present in Tables 62, 63 and 64 suggested plans of treatment for use in various types of cardiovascular syphilis. It should be clearly

TABLE 62

SUGGESTED OUTLINE OF TREATMENT FOR UNCOMPLICATED SYPHILITIC AORTITIS

Weeks	Treatment	Remarks	General medical care
1–12	12×0.2 gm. bismuth subsalicylate. KI gms. 2 t.i.d.	Preparatory heavy metal to avoid possible Herxheimer (coronary occlusion)	Bed rest and digitalis not necessary unless cardiac failure is present. If it is, or if it develops later see outline for aortic insufficiency and aneurysm.
13–20	8×neoarsphenamine or mapharsen	First injection small dosage (0.2–0.3 gm. neoarsphenamine or 0.030 gm. mapharsen). Do not exceed 0.6 gm. neoarsphenamine or 0.060 gm. mapharsen.	
21–32	12×0.2 gm. Bi. KI	Symptomatic relief usually prompt.	
33–42	10×0.6 neoarsphenamine or 10×0.040–0.060 mapharsen	Neoarsphenamine probably preferable—fewer reactions. Smaller doses may be necessary if signs of circulatory embarrassment are present.	If necessary for pain, use amyl nitrite, nitroglycerin, or theobromine derivatives with phenobarbital. Examine the urine periodically
43–54	12×Bi. KI	Test C.S.F. now or earlier to see if complicating neurosyphilis is present. If so, consider change in therapy (tryparsamide, fever)	
55–64	10×neoarsphenamine or mapharsen	Re-examine heart at frequent intervals. Watch for progression of lesion, especially the development of aortic insufficiency	Repeat roentgenologic studies at least once a year
65–104	Disregard the results of serologic tests in the blood. Seroresistance is common. Continue as above, with courses of an arsenical alternating with courses of bismuth and KI. Rest periods are undesirable, but may be permitted if necessary, especially just after a heavy metal course.		
Thereafter	Follow the patient for the remainder of his life with periodic physical and x-ray examinations. Renew treatment with recrudescence of symptoms or physical evidence of progress, as above. In any case give an occasional course of treatment (once a year or thereabouts)—a course of heavy metal followed by a course of an arsenical.		

understood that these outlines are intended to serve only as an expression of principles, and that they are not to be followed so rigidly as to exclude modifications required by the particular circumstances of the individual patient.

TABLE 63

SUGGESTED OUTLINE OF TREATMENT FOR ANEURYSM OR AORTIC REGURGITATION IN THE ABSENCE OF CONGESTIVE HEART FAILURE

Weeks	Treatment	Remarks	General medical care
1–10	10 × Bi. 0.2 gm. KI gms. 2 t.i.d.	To avoid the Jarisch-Herxheimer reaction and therapeutic paradox.	Bed rest for 3–4 weeks not essential but desirable.
11–20	10 × neoarsphenamine 0.1–0.3 gm. or 10 × mapharsen 0.010–0.030 gm.	Start with minute doses. Do not exceed 0.3 gm. neoarsphenamine or 0.030 gm. mapharsen and reduce dose or change drug if reactions occur	Restrict physical activity at once and permanently
21–32	12 × Bi 0.2 gm. KI gms. 2 t.i.d.	Symptomatic relief is more prompt in aneurysm than in aortic regurgitation, where it is often slow. Have patience!	Digitalis unnecessary unless heart failure present but failure perhaps may be forestalled by administration of digitalis at first appearance of mild exertional dyspnea.
33–42	10 × neoarsphenamine 0.1–0.3 gm. or 10 × mapharsen 0.010–0.030 gm.	Unless clinical signs of neurosyphilis are present, test C.S.F. only if convenient. The C.V. situation is more serious than asymptomatic neurosyphilis.	Two weeks in bed every year will do no harm and may help.
43–54	12 × Bi. 0.2 gm. KI gms. 2 t.i.d.	Watch patient constantly for impending cardiac failure—tachycardia, dyspnea, edema. If it occurs, bed rest!	Avoid all possible physical stress.
55–64	10 × neoarsphenamine 0.1–0.3 gm. or 10 × mapharsen 0.010–0.030 gm.	Disregard results of serologic tests. Seroresistance is common.	Reduce tobacco in excessive smoking. Avoid alcohol. Examine the urine periodically
65–104	Continue as above, with courses of neoarsphenamine or mapharsen alternating with courses of a heavy metal and KI. Rest periods are undesirable but short ones (not to exceed 6 weeks) may be permitted if essential. Avoid all treatment reactions, reduce dosage if they occur or change drugs.		
Thereafter	In many patients, especially if symptoms persist, treatment may profitably be continued, perhaps indefinitely. Careful follow-up—periodic physical and x-ray examinations. Renew treatment if symptoms reappear		

TABLE 64
SUGGESTED OUTLINE OF TREATMENT FOR CARDIOVASCULAR SYPHILIS IN THE PRESENCE OF CONGESTIVE HEART FAILURE

Weeks	Treatment	General medical care
1 ? (usually 6 or 8) until cardiac compensation is stabilized at the best attainable level.	KI only until compensation is regained. If gross edema is present, salyrgan or mercupurin 0.05–0.1 gm. daily I V or mercury succinimide 0.01 gm. daily I.V or I.M	Full bed rest, in hospital if possible, until compensation is regained and stabilized. Morphine essential in the acute phase. Full digitalization and its maintenance Prolonged rest, with slow return to limited activity by graduated exercise. Special measures (e.g thoracentesis, oxygen tent) as indicated
Thereafter if satisfactory cardiac compensation is regained.	Bismuth subsalicylate 0.1 gm. every 4–5 days for 3–4 doses. Then bismuth subsalicylate 0.2 gm weekly for a total of 12 weeks, followed by weekly injections of mapharsen 0.005 gm. increasing to 0.03 gm., or neoarsphenamine 0 06 gm. increasing to 0.3 gm or bismarsen 0 1 gm. increased to 0 2 gm. Thereafter as in Table 63.	Permanent maintenance of full digitalization. (Frequently 0.1 gm. of the powdered leaf daily but considerable variation in patient s requirements and tolerance. Individualize!) Permanent restriction of physical activity to the absolute minimum, not the maximum apparently tolerated
Or thereafter if satisfactory cardiac compensation is not regained	Bismuth subsalicylate as above, alternating with mercury by inunction for 6 weeks and rest periods of 2–3 months. Avoid arsenicals entirely	As above. Another episode of grave decompensation always to be feared.

Roughly the absence of pulmonary congestion or periph ral edema the capacity to sleep in a normal position and the ability to lead a sedentary life without breathlessness

The treatment of associated cardiovascular and neurosyphilis—Neurosyphilis is a common complication of cardiovascular syphilis and *vice versa*. Among our own patients with aneurysm or aortic regurgitation 17 per cent had associated clinical evidence of neurosyphilis the majority tabes. Under these circumstances it is the physician s province to evaluate which type of involvement is productive of the greatest discomfort incapacity and risk to life. In most instances cardiovascular syphilis is much more to be feared as a probable cause of death. Here the problem is to find a method of treatment which will ameliorate distressing symptoms of neurosyphilis, and which at the same time will be of benefit from the cardiovascular standpoint without doing harm. Often the type of *relatively mild treatment suggested for cardiovascular syphilis* will benefit the neurosyphilis also If not tryparsamide may be employed in aver

age therapeutic dosage (1 0–3.0 gms) This drug has no deleterious effect analogous to those of the trivalent arsenical compounds in cardiovascular syphilis on the other hand it is probably of no particular value in con trolling progression of the cardiovascular lesion. In the special cases concomitant treatment with tryparsamide and bismuth, each to be given weekly in usual dosage may best serve to deal with a difficult situation. Where indicated (Chapters XXIII and XXIV) heterologous arsphenaminized serum may be given intraspinally with no untoward effects.

Occasionally one encounters a patient with cardiovascular syphilis coincident with tabes dorsalis and rapidly advancing optic atrophy or with dementia paralytica. Here the neurosyphilitic lesion will lead unless properly dealt with, to hopeless incapacity from blindness on the one hand, or to death on the other In such a situation, the risk of fever therapy and the chance of benefit to be derived from it must be carefully weighed against the gravity of the situation. There is natural reluctance to induce therapeutic fever in patients with outspoken cardiovascular disease. In the special case, however in which on proper indication the risk is assumed patients with outspoken cardiovascular disease frequently tolerate fever therapy surprisingly well, especially if quartan malaria be used.

The frequent association of vascular neurosyphilis with cardiovascular syphilis is probably on the basis of widespread vascular involvement. No intensification of antisyphilitic treatment should be attempted in such patients and, as a matter of fact, in any type of neurosyphilis intensification of arsphenamine therapy past the point advisable from the standpoint of the circulatory apparatus calls for great caution.

The surgery of cardiovascular syphilis —Saccular aneurysms of peripheral arteries in the extremities should be managed by a combination of surgery and antisyphilitic treatment. One of the forms of aneurysmorrhaphy is usually desirable. These operations largely developed by Matas and described in standard surgical texts are calculated to cure the aneurysm by (1) closure of the opening from the vessel into the sac (2) plastic operation for reconstruction of the vessel lumen or (3) the obliteration of the sac by suture.

Wiring and electrolysis of thoracic and abdominal aneurysms to obliterate the sac by intramural clotting, has been recently reviewed by Penick. The procedure may be of value in certain large aneurysms presenting close to or eroding the chest wall

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Chapter XIX

THE TREATMENT OF VISCERAL SYPHILIS

The proper management of visceral syphilis depends as much on accurate differential diagnosis as on the application of treatment methods. Except in barest outline, a discussion of diagnosis is obviously beyond the scope of this monograph and for details the reader should consult a more comprehensive text, such as that of Stokes or the monumental Handbuch. With certain exceptions the principles of treatment are those of late syphilis in general (Chapter XV) In addition to specific chemotherapy however adjuvant medical or surgical measures are often essential.

The Treatment of Syphilis of the Larynx, Trachea and Bronchi

The avoidance of the Herxheimer reaction is of first importance in gummatous laryngitis. If treatment is started with an arsenical the sudden increase in inflammation and edema in the local lesion may lead to complete laryngeal obstruction and necessitate an emergency tracheotomy or if this operation is not performed to death by suffocation. We have seen two patients in whom the injudicious initiation of treatment with a large dose of arsphenamine made emergency tracheotomy obligatory In all patients with gummatous laryngitis the first 10 days or so of treatment should be carried out in the hospital where constant supervision is possible. The initial course should consist of a heavy metal and potassium iodide prolonged for at least 4 weeks before arsenical therapy is attempted. Thereafter treatment may proceed as in any patient with uncomplicated late syphilis though the first dose of an arsenical should be small (arsphenamine 0 1 gm. neoarsphenamine 0.3 gm mapharsen 0 03 gm)

Syphilis of trachea and bronchi while rare is encountered much more frequently than pulmonary syphilis (Conner) Theoretically therapeutic shock should be a danger here also although it has not seemed important in the few patients we have seen In healing the ulcerative lesions in trachea and great bronchi may produce a degree of stenosis incompatible with respiratory comfort. In such patients some degree of relief may be obtained by cautious dilatation by a skilled bronchoscopist.

The Treatment of Pulmonary and Mediastinal Syphilis

Both of these conditions are rarities We have seen only one case of pulmonary syphilis which fulfilled the rigid clinical and pathologic criteria of diagnosis though a half dozen patients with gummatous mediastinitis and obstruction of the superior vena cava have passed through our clinic. The clinical diagnosis of pulmonary syphilis rests largely on the demonstrated absence of pulmonary tuberculosis, fungus infection or

tumor and the prompt disappearance of the lesion after the institution of antisyphilitic treatment.

The great difficulty of clinical differentiation between pulmonary syphilis and tuberculosis raises again the question of therapy when tuberculosis and syphilis are associated in the same patient. This has already been discussed so far as early syphilis is concerned in Chapter XIV. Padget and Moore present a discussion of the problem in late syphilis which is briefly summarized here. (1) In long-standing syphilitic infection without evidence of clinical progress but with a recent active pulmonary tuberculosis, antisyphilitic treatment had better be postponed until the tuberculous process has become apparently arrested, and even then, carried on only with intermittent courses of mercury or bismuth, without the use of arsphenamines or the iodides. Mercury by inunction is the safest method of treatment. The coexistence of syphilis does not contraindicate therapeutic pneumothorax, or surgical procedures for lung collapse. (2) When a long-standing syphilitic infection is complicated by inactive fibroid tuberculosis, antisyphilitic treatment, including the arsenicals, may be employed but less intensively than in non-tuberculous patients. Fever therapy, especially malaria, should be avoided except in the case of paresis, when the risk of lighting up the quiescent tuberculosis must often be accepted.

The prognosis of untreated pulmonary syphilis is more grave than one would expect. In an analysis of 95 such cases, one personally observed and the remainder collected from the literature, Takei found a mortality of 34 per cent. When treated early, the outcome was in most instances satisfactory. There is no contra-indication to any desired form of treatment which should be managed as for late syphilis in general. When the therapeutic test is depended upon to differentiate pulmonary syphilis and tuberculosis, it should be carried out with small doses of neoarsphenamine or mapharsen and without the iodides, in order to avoid a possible spread if the lesion proves to be tuberculous. Frequent control of treatment by repeated x-ray of the chest is, as pointed out by Lacaze in a presentation of 2 personally observed cases and 17 additional ones collected from the literature, essential.

In mediastinal syphilis, therapeutic shock (the Herxheimer reaction) is to be avoided because of the potential danger of suffocation from increased pressure within the closed thorax. The first few months of treatment should be carried out with the heavy metals and the iodides, the arsenicals being avoided until evidence of definite improvement has appeared. Thereafter, no special precautions are necessary.

The Treatment of Gastric Syphilis

The most important contribution of recent years to this confused subject is the convincing demonstration by Stokes and Brown and by Friedenwald and Morrison that "stomach trouble" in the syphilitic patient is rarely caused by gastric syphilis, and infrequently is due to any organic lesion of the gastro-intestinal tract. On the contrary, the apparent exciting cause in 75 per cent of such patients lies entirely outside the gas-

tro-intestinal apparatus in the nervous system. The moral of these observations with which we fully agree is that in the syphilitic patient with stomach trouble a neurologic examination and study of the spinal fluid are indicated even before the more usually tried gastric analysis and barium x-ray series.

As to the treatment of actual gastric syphilis we find ourselves unable to report any detailed personal results either because gastric syphilis in our clientele is exceptionally uncommon or because of our own inability shared by other members of *our staff to recognize the lesion when it* exists. Our experiences with the diagnosis of gastric syphilis have been unfortunate in that almost all the patients in whom we have suspected this lesion have disappeared from observation before confirmation could be obtained, or have ultimately been found at operation or necropsy to have some other lesion, usually either simple ulcer or carcinoma. Our experience is limited to about a dozen cases diagnosed by biopsy at operation. The autopsy records of the Johns Hopkins Hospital contain only a very few cases regarded pathologically as gastric syphilis and the rarity of this condition is illustrated further by the fact that the literature contains only one indubitably proved example (Harris and Morgan) Williams however rightly points out that the demonstration of treponemes by animal inoculation is not a requirement for the diagnosis of other lesions of late syphilis and, with Carter believes that the diagnosis of *syphilis of the stomach may be made clinically if certain criteria are ful*filled. They are (1) the age of the patient (syphilis of the stomach usually appears before the age of 40) (2) collateral evidence of syphilis (3) roentgenologic evidence of the presence of an annular tube-like prepyloric constriction (4) improvement under antisyphilitic treatment and (5) the discovery at operation *if performed of an inflammatory mass* microscopically compatible with syphilitic inflammatory tissue.

The Mayo Clinic has been interested in this field for years and the latest report of their collected series of cases now comprises 93 of which 10 were verified at operation. The most difficult differential diagnosis is between gastric carcinoma and syphilis Here opinion differs as to the immediate procedure. The Mayo Clinic group feels that the estimation of the response to antisyphilitic treatment in conjunction with a prolonged period of observation offers the most practical method of arriving at a diagnosis of gastric syphilis. We in agreement with others (Priestley and Walters and Pusch) favor immediate exploratory laparotomy unless x ray studies show the lesions to be certainly inoperable. The reasons for this are that an exploratory operation entails in itself little or no risk that the only hope of cure of gastric carcinoma now available is early diagnosis and radical resection before metastasis has occurred that if operation is delayed for the several weeks or months necessary for the performance of a therapeutic test, an operable carcinoma may be converted into an inoperable one and that if the lesion proves to be syphilitic treatment will be as effective after operation as before. In fact, we are so strongly impressed by the difficulty of differential diagnosis that we believe the tentative clinical impression of gastric syphilis is an imperative indication for immediate exploration.

Eusterman very properly stresses the fact that if the gastric lesion is shown at operation to be syphilitic, radical resection is unwise, certainly until post-operative antisyphilitic treatment has been given a thorough trial. The danger of development of pernicious anemia after complete gastric resection (Poole and Foster and Singer and Steigmann) must not be forgotten. Experience with numerous exploratory laparotomies has made us feel however that the surgical diagnosis should rest not on mere inspection and palpation of the stomach but on excision of a fragment of the lesion large enough to establish histologic or biologic verification.

Whether performed before or after operation a therapeutic test for gastric syphilis should be carried out "in the hospital under close observation where the intake of food can be measured and the same type of diet can be maintained throughout the test. When possible, the patient is given a general mixed diet, and if the gastric capacity is markedly reduced the daily ration is divided into from four to six meals instead of the customary three. A daily record of weight is maintained and frequent estimations of the degree of anemia and its variations are made. Medication, other than antisyphilitic remedies, is discontinued (O'Leary) Arsphenamine, in doses of from 0.2–0.5 gm. is given weekly since the danger of a Herxheimer reaction is absent, and, coincidentally bismuth or mercury may also be given. It is unwise to attach too much significance to early relief of the gastric symptoms since non-specific improvement, often striking may occur in carcinoma or simple ulcer A persistent and steady gain in weight, accompanied by a decrease of the anemia, and the ability to eat larger amounts of food with less discomfort are of more significance than changes in the patient's subjective complaint." O Leary insists that a positive therapeutic test involves not only these criteria, but the maintenance of improvement for at least 2 years. It is hardly necessary to add that if exploratory operation and subsequent therapeutic test have established the syphilitic nature of the gastric lesion treatment should be continued, as in any other patient with late syphilis, for a minimum period of 15–24 months

The results of operation and antisyphilitic treatment in the Mayo Clinic cases are summarized in Table 65. All writers emphasize the facts that clinical and roentgenologic improvement may not coincide restoration to anatomic normality is uncommon. Lack of improvement may be

TABLE 65

THE RESULTS OF TREATMENT IN 93 PATIENTS WITH GASTRIC SYPHILIS (AFTER EUSTERMAN)

Outcome	Per cent
Clinically "cured"	36 5
Much improved	42 5
Some benefit	11 0
No improvement	10 0

Number or percentage of deaths not stated, though O Leary reporting on 89 of these cases, says 7 per cent (6 patients?) are dead.

due to contraction of the stomach wall as a result of scarring, which embarrasses the patient by virtue of small stomach capacity "In this type of patient, neither continued antisyphilitic treatment nor plastic surgery offers relief

The Treatment of Hepatic Syphilis

In this country and largely abroad, the treatment of syphilis of the liver has been influenced by the work of McCrae (1912 1926) Wile (1922) *Stokes (1926) and O'Leary and his associates (1929)* In their latest paper O'Leary Greene and Rowntree discuss treatment on the basis of the following classification

1 Benign hepatitis of early syphilis
2. Acute yellow atrophy in early syphilis
3 Asymptomatic late hepatic syphilis
4. Diffuse hepatitis of late syphilis
5 Gummatous hepatitis
6 Chronic hepatitis or syphilitic cirrhosis
   (a) with jaundice (biliary cirrhosis)
   (b) with ascites (portal cirrhosis)
7 Hepatic complications of treatment for syphilis
   (a) Post-arsphenamine jaundice
   (b) Post-arsphenamine acute yellow atrophy
   (c) Hepatorecurrence and Herxheimer effect on the liver
   (d) Treatment cirrhosis
   (e) Jaundice associated with therapeutic malaria.

Our comments are based on a study of some 200 cases in the Johns Hopkins Hospital diagnosed clinically or pathologically as hepatic syphilis, as well as on a survey of the literature.

The treatment of early hepatic syphilis —The infrequency with which this problem arises is illustrated by the low incidence of jaundice in association with untreated early syphilis in our clinics. Clinical evidence of hepatic damage occurs not oftener than 1 in 1 000 recently infected patients and we have never observed an example of acute yellow atrophy in untreated early syphilis. In the three or four patients we have seen with benign early hepatitis (jaundice) arsphenamine has been given at the start of treatment just as in uncomplicated early syphilis. In every instance the jaundice rapidly cleared there were no evidences of decreased tolerance for the arsenicals and the patient s subsequent progress was uneventful. Waugh who has had identical experiences, agrees that there is no reason for caution in the use of arsenical drugs in this situation.

In early acute yellow atrophy the prognosis while poor is said to be better than when the lesion is due to other causes. Wile reports a case and mentions others in which recovery followed intensive treatment. Most writers advise arsphenamine though the condition is so rare that few if any observers have seen more than a single case.

The diagnosis and clinical differentiation of late hepatic syphilis and its relation to treatment —It has been generally assumed since the publication of McCrae s figures of incidence of hepatic syphilis

(1.5 per cent of 3,300 necropsies 0.2 per cent of clinical diagnoses among 27 000 medical admissions) that involvement of the liver is frequent in late syphilis, and indeed, that it ranks next after involvement of the central nervous system and cardiovascular apparatus. Estimates of its frequency vary from 2 per cent (O Leary) to 10 per cent (Stokes) Stokes makes ingenious use of McCrae s data, and of the incidence of palpable livers in patients with late syphilis, to set up a classification of asymptomatic hepatic syphilis—the "latent liver" As a matter of fact, and on the basis of a survey of the clinical and necropsy material of the Johns Hopkins Hospital covering 32 years, hepatic syphilis is much less frequent than we had supposed. A critical review of the material shows that only 33 cases have occurred among 8 500 necropsies in adults and the clinical diagnosis has been made only 34 times among 6 420 patients with late syphilis. Its clinical diagnosis is often extraordinarily difficult and subject to a wide margin of error in mistakes both of omission and commission. On the basis of this survey carried out by Goodman and Moore we believe that the diagnosis of hepatic syphilis is never justifiable on the basis of a palpable liver alone in the absence of other symptoms or signs and that while asymptomatic hepatic syphilis may conceivably exist it is rare and completely unrecognizable on clinical grounds. Furthermore it is difficult, if not impossible, to differentiate on clinical grounds between isolated gumma of the liver and diffuse syphilitic hepatitis except on the one single basis of the presence or absence of ascites. If this symptom of portal obstruction is present, one may be reasonably sure that the lesion is diffuse even though isolated nodular masses are palpable. Its absence however does not indicate that the involvement is not diffuse since even without ascites a single large gumma may be surrounded by clinically undetectable miliary gummatous nodules scattered through the entire liver parenchyma. In most instances therefore, the only differentiation into type capable of being made clinically is the major subdivision of (a) relatively acute inflammatory (gummatous) involvement sometimes isolated but usually diffuse and (b) chronic hepatitis with advanced cirrhosis Chapman Snell and Rowntree feel however that early cirrhotic lesions may be recognized with some degree of accuracy

The importance of all this in relation to treatment lies in the question of the use of the arsenical preparations *versus* other less intensive treatment methods. Wile's discussion of the therapeutic paradox, as applied to the syphilitic liver has influenced syphilotherapists everywhere. His argument, briefly summarized is as follows:—brilliant results are occasionally achieved in syphilitic hepatitis, especially when this is of the isolated gummatous type by energetic treatment including the arsenicals. In patients with diffuse interstitial hepatitis however an apparent paradox occurs in that the patients improve with regard to syphilis and get worse or die of cirrhosis. "The end result of all syphilitic processes is a fibrosis. The process of repair in a parenchymatous organ in which fibrosis is going on depends on its ability to recuperate by hypertrophy or by reproduction of its substance. The latter two functions are distinctly slow processes. Treatment therefore, directed to a diseased organ

in which the inevitable and ultimate result both of the disease and of the treatment is the production of a scar, should be of a type which leads to a slow rather than a rapid process of repair' For this reason and also because of the possibility that the drug itself might produce further damage in an already diseased liver Wile believes that the arsenicals have no place in the treatment of hepatic syphilis. This opinion is completely shared by McCrae, and to a lesser extent by Stokes O'Leary, and others.

A study of the Johns Hopkins material provides interesting information as to these important points Leaving aside for the moment the group of patients with definite atrophic (Laennec s) cirrhosis and portal obstruction and limiting the discussion to those patients with the clinical picture of relatively acute gummatous (isolated or diffuse) hepatitis two facts stand out. First we have given an arsphenamine at some time during treatment to some 50 patients with hepatic syphilis Of these one died of acute yellow atrophy of the liver appearing immediately after the tenth injection of neoarsphenamine one developed a mild post-arsphenamine jaundice with prompt and complete recovery We concur therefore in the opinion that there is some added risk in giving arsphenamine products to patients with livers already extensively involved by syphilis.

Second the therapeutic paradox described by Wile has been of negligible importance in our clinic In his experience it has been a common occurrence for a patient with syphilitic hepatitis to develop his first ascites following the administration of arsphenamine. In our series this phenomenon has been observed but once and even this was doubtful since some observers thought that this particular patient had ascites before treatment was started. Indeed of 8 patients treated exclusively with heavy metal and potassium iodide in our series, only 2 are now living and 6 are dead while of 20 who received an arsphenamine at some time during treatment, 15 are living and only 5 are dead.

It seems to us that the poor results in certain patients with hepatic syphilis depend not so much on treatment whether with or without an arsenical, as on the type and extent of hepatic damage before treatment is started. The only signpost of value in determining the gravity of the pre-existing lesion appears to be the presence or absence of sufficient diffuse involvement to cause portal obstruction and ascites If this is not present, the prognosis is good if it has occurred the prognosis is poor under any form of treatment Functional tests, such as serum bilirubin determinations levulose tolerance, or dye retention (bromsulphalein) tests do not yield as much information as this single simple clinical criterion.

The summary of treatment in 28 well followed patients presented in Table 66 shows clearly the difference in ultimate outcome in patients with and without ascites. Interestingly enough these data are almost the exact duplicate of the treatment results furnished by Stokes. All the deaths in our series are attributable to hepatic syphilis except one a patient in the 'no ascites group who died of typhoid fever Of the 10 patients with ascites 6 were treated only with a heavy metal and potassium iodide of these 4 are dead. All except two of the 18 patients without ascites re-

TABLE 66

THE OUTCOME OF TREATMENT IN SYPHILIS OF THE LIVER

	Total patients	Living and well	Living invalided	Dead
Ascites present before treatment	10	1	2	7
No ascites before treatment	18	12	2	4
Total	28	13	4	11

ceived an arsphenamine at some time during treatment one of the 4 deaths occurred in a patient who received no arsphenamine but only heavy metal and iodides. The number of injections of arsphenamine administered varied from 1 to 72, and averaged 20 On the basis of this experience, therefore we do not share the prevalent fear of the arsenicals, provided their use is limited to patients with gummatous hepatic syphilis without evidences of portal obstruction. In fact in such circumstances we think their use is strongly indicated and that the slight added risk of increased hepatotoxicity should be accepted.

The initiation of treatment in gummatous hepatic syphilis without ascites —Perhaps our relative freedom from experience with the therapeutic paradox is due to the fact that for many years it has been customary in our clinics to initiate treatment in hepatic syphilis with a period of 10–16 weeks' use of bismuth or mercury together with potassium iodide. This serves also as an adequate therapeutic test in patients in whom the diagnosis is suspected but in whom such other possibilities as cholecystitis gall-stones carcinoma, etc. exist. Fever jaundice subjective discomfort usually disappear within a week or two and a palpable mass may shrink as if by magic.

Continuation of treatment —If during this initial period of heavy metal and iodide therapy there is prompt subjective and objective improvement, and if ascites has not appeared the use of an arsenical preparation may be cautiously started. Neoarsphenamine or mapharsen are the drugs of choice the dosage should be small at first, gradually increasing to the desired maximum. If this is tolerated without reaction treatment should be prolonged until the equivalent of two full years of continuous treatment has been given alternating between arsenical and heavy metal courses. Rest periods may be interpolated if desired after the first 6 months, but, if this is done, the total duration of treatment should be prolonged so that, no matter over what period of time it may extend, a full 24 months of treatment is given. Serologic progress may be disregarded seroresistance is the rule.

The complications of gummatous hepatic syphilis —At one other point we find ourselves at variance with much published experience with hepatic syphilis The statement is frequently made that involvement

of other structures or systems by syphilis is uncommon in patients with syphilis of the liver In more than half of our patients there were definite lesions elsewhere in the body, most commonly in the cardiovascular apparatus. When this is true further treatment after the initial course of heavy metal and iodide may be more materially influenced by the complication than by the lesion in the liver

As Stokes points out, associated renal damage, amyloid or otherwise is fortunately rare in patients with hepatic syphilis.

The treatment of gummatous hepatic syphilis with ascites — Our own experience, as well as that of others indicates that with any form of treatment, the prognosis in this condition is uniformly poor The death rate is high and even if the patient survives the best he can usually look forward to is a life of chronic invalidism In this group of patients our experience with the use of arsphenamines is too limited to be of value but on the basis of the testimony of others we are prepared to concede that the arsenicals may do more harm than good and to avoid them entirely Reliance must be placed on the heavy metals and the iodides. A patient persistent trial of treatment over a period of several months should always be made since occasionally one is surprised by the rapidity degree and permanency of improvement.

Withdrawal of ascitic fluid by paracentesis is inadvisable until after a thorough trial of rest in bed restriction of fluids saline or hydragogue catharsis, and the use of one of the mercurial diuretics (salyrgan) In many patients the ascites may be controlled by these means. Paracentesis is not without risk of precipitating a 'liver crisis i.e. death in a few hours or days from an apparently overwhelming toxemia and once started it must usually be continued. We have one unfortunate patient who has now undergone more than 150 tappings with the almost weekly withdrawal of 5–10 liters of fluid.

The treatment of syphilitic cirrhosis of the liver—There is a group of patients fortunately small, in whom the clinical picture even at the onset is that of atrophic (Laennec's) cirrhosis of the liver The syphilitic etiology of the cirrhosis is suggested by the associated positive serologic tests. The pre-existing gummatous infiltration whether isolated or diffuse, has passed unrecognized perhaps because symptomless clinical evidence (fever chills, etc.) that the lesion is inflammatory is usually lacking the first warning of impending trouble is the appearance of symptoms of portal obstruction.

In this type of hepatic syphilis our own experience indicates that treatment of any sort, whether with an arsenical preparation the heavy metals or the iodides is without avail in arresting the downhill progress of events. Goodman and Moore have compared the average duration of life, dating from the appearance of ascites in 13 patients with non-syphilitic cirrhosis with that in 12 patients with syphilitic cirrhosis (in all instances proved at necropsy) the patients of the former group lived on the average for 8 months of the latter for 9 months. In the majority death followed within 4–6 months of the appearance of symptoms regardless of therapy

Chapman Snell and Rowntree are less pessimistic than ourselves over

either the possibility of the early diagnosis of compensated syphilitic cirrhosis (i.e. before the development of ascites), or of the results of treatment before or after the appearance of ascites. They report 10 patients with compensated and 13 with decompensated cirrhosis thought to be syphilitic in origin. Of the former only one is dead nine are living in fairly good health years after the original diagnosis (exact length of observation not stated) Among the latter the results are not definitely given but the average duration of life after the onset of ascites probably exceeded 16 months, and two patients have lived 10 and 12 years respectively

Since in any individual patient there may be considerable difficulty in arriving at a decision as to how large an inflammatory element may be present in the lesion, it is always worth while cautiously to try antisyphilitic treatment, always with the heavy metals and the iodides never with the arsenicals. Alcohol, as shown by the pathologic study of Schumacher should be strictly forbidden. The prolonged use of large doses of the vitamin B complex may be helpful. If symptomatic improvement is not obtained within 3 months, further efforts should be abandoned and subsequent treatment should be symptomatic only (Rowntree, Keith, and Barrier)

The hepatic complications of treatment for syphilis.—Postarsenical jaundice and acute yellow atrophy have been discussed in detail in Chapter VII.

Hepatorecurrence and Herxheimer effect in the liver.—These two explanations have been offered by Milian as possible causes for most instances of supposed post-arsenical jaundice. More recently they have been discussed by Greenbaum and by O'Leary Greene and Rowntree. It is suggested that in patients with asymptomatic hepatic syphilis the initiation of treatment with arsphenamine may cause the sudden appearance of jaundice due to a Herxheimer reaction in the diseased liver tissue. If this occurs it should appear early in the course of treatment i.e. after the first or second injection of the drug. Though this is theoretically possible, we have never seen a case.

Although Milian and others apply the use of the term hepatorecurrence to the appearance of jaundice enlarged liver etc., appearing within a few days after an injection of an arsphenamine we cannot conceive that this explanation is correct. We have never seen an example of the appearance of hepatic syphilis in the midst of treatment and do not believe that it occurs. To our mind the term hepatorecurrence implies only the development at a considerable interval (months or years) after the inadequate treatment of early or late syphilis, of definite hepatic syphilis. It seems to us that no special name for this condition is required.

Treatment cirrhosis is described and a supposed case reported by O'Leary and his associates, who believe this is an occurrence of increasing frequency They stress the possible effect of prolonged arsphenamine treatment in producing cirrhosis influenced perhaps by their earlier experience with portal cirrhosis associated with chronic inorganic arsenical poisoning Neither their report nor that of Baldridge is convincing. There

is no reason why syphilitic patients should not develop atrophic cirrhosis, whether caused by alcohol or by other factors producing this condition in as high a proportion as non-syphilitic patients We have never seen an instance of atrophic cirrhosis in which antisyphilitic treatment seemed to be responsible and as a matter of fact would not know how to differentiate between treatment cirrhosis and the pure coincidence of non-syphilitic Laennec's cirrhosis Certainly, *since cirrhosis of the liver is so extremely* uncommon in patients who receive vast quantities of antisyphilitic drugs it cannot be regarded as a serious risk of treatment.

Jaundice associated with therapeutic malaria is discussed in Chapter XXIII.

Surgical procedures in hepatic syphilis—The confusion of diagnostic possibilities in suspected hepatic syphilis often necessitates early surgical consultation. Contrary however to the situation in suspected gastric syphilis the therapeutic test takes preference over surgical exploration, except in those instances in which the acuteness of the patient's illness suggests liver abscess or suppurative cholecystitis If improvement, both subjective and objective does not occur after a 2–3 months trial of antisyphilitic treatment, exploratory laparotomy should be undertaken.

Stokes discusses splenectomy in patients with hepatosplenic syphilis especially in those with Banti's syndrome (which has been limited in our experience to congenital syphilis) mentions four patients in whom the operation was carried out with good results in two, but is unenthusiastic because of the high operative mortality and the uncertainty of the outcome. We have seen only one patient in whom splenectomy seemed advisable. This patient died shortly after operation Korns feels as do we that antisyphilitic treatment of syphilitic patients with Banti's syndrome is often productive of spectacularly good results indeed, he goes further and thinks that a therapeutic test is justifiable in every patient with Banti's syndrome even if other evidence of syphilis is lacking.

Bleeding esophageal varices are a frequent cause of death in patients with syphilitic cirrhosis of the liver Walters Rowntree, and McIndoe have suggested the surgical procedure of ligation of the coronary veins in this condition. Experience with this operation is as yet too incomplete for adequate comment. It might certainly be tried in patients who survive the first attack of hematemesis.

Omentopexy (the Talma-Morrison operation) for relief of ascites has been carried out in several patients in our series with uniform poor results. Rowntree thinks this operation might be more successful if done *early before the development of ascites.*

The Treatment of Syphilis of the Spleen

Except for the splenic enlargement which accompanies hepatic syphilis either in congenital syphilis as part of Banti's syndrome or in acquired syphilis as one evidence of portal obstruction syphilis of the spleen in our experience is extremely rare. We have seen two instances of huge splenic gummas apparently unassociated with hepatic involvement. In both in-

stances there was rapid disappearance of the splenic tumor under arsphenamine therapy

The Treatment of Rectal Syphilis

One of the interesting advances of modern medicine is the demonstration that stricture of the rectum formerly thought almost always to be due to syphilis is actually rarely due to this cause. Much more frequently is it the result of lymphogranuloma venereum or less often of gonorrheal or tuberculous pelvic inflammatory disease ulcerative colitis endamebiasis, or trauma (Rankin and associates Sulzberger and Wise) As a matter of fact though rectal stricture is common in the clientele of our clinic especially among Negresses, we cannot recall ever having seen a case in which its syphilitic etiology was indubitably proved. We have recently seen a probable but unfortunately not proved case of ulcerative gummatous lesions of the rectum.

Even if the lesion is sometimes due to syphilis the results of antisyphilitic treatment are invariably disappointing. The stricture is due to the contraction of scar tissue, which no type or amount of chemotherapy will relieve Though antisyphilitic treatment should unquestionably be given to syphilitic patients with rectal stricture relief from the local symptoms must depend on the surgical procedures of dilatation, colostomy or ileostomy

The Treatment of Anemias Associated with Syphilis

Cummer has presented a splendid summary of this subject. All other possible causes must be excluded before making a diagnosis of syphilitic anemia. Syphilis is much more often coincidental than causative There is no evidence that syphilis may produce an anemia of pernicious type. Secondary anemia, usually mild may appear at any stage of syphilitic infection but is particularly frequent in association with aortic, gastric or hepatic syphilis. In hepatosplenic syphilis associated with either acquired or congenital syphilis (much more frequently the latter) the anemia may assume the picture characteristic of Banti s syndrome.

The secondary anemia occurring in early constitutional syphilis usually responds well to routine antisyphilitic treatment. No special precautions to guard against reactions are necessary In late syphilis the prognosis of the anemia depends upon the associated organic disease. It is generally agreed that antisyphilitic treatment in the presence of a severe anemia, whether primary or secondary should be carried out with great caution. Small doses of the arsenicals are preferable to the heavy metals which in themselves may cause anemia.

In the event of the association of pernicious anemia and late syphilis it is usually desirable to postpone antisyphilitic treatment until the blood has been brought up to normal by liver therapy Thereafter there is no contra-indication to the administration of arsphenamine or heavy metal in average dosage In patients with secondary anemia the cause if apparent should be eliminated and iron (ferric ammonium citrate by mouth

Murphy) and if necessary transfusion, should be used in association with mild antisyphilitic treatment.

Paroxysmal hemoglobinuria is usually it not always, associated with congenital syphilis Its existence does not contra-indicate energetic antisyphilitic treatment, and the results are usually excellent. We have seen five patients in whom a complete cure was obtained Mackenzie has observed three others and Kumagai and Namba report cures in 10 of 14 cases.

The Treatment of Syphilis with Associated Diabetes, Pancreatic Syphilis

Syphilitic diabetes is a great rarity though the association of diabetes and syphilis is frequent. Joslin's enormous material contains not a single case of proved syphilitic diabetes. We have seen only one patient in whom antisyphilitic treatment seemed to exercise any effect whatever in improvement of lowered carbohydrate tolerance However the existence of diabetes provided it can be controlled with diet and insulin, need not interfere with treatment for syphilis of any desired type and intensity There is no indication that the arsenicals and heavy metals are less well tolerated by diabetic than by normal persons Whether or not antisyphilitic treatment is to be given to such a patient and if so its character and intensity will depend on a study of such factors as the severity and controllability of the diabetes the patient's age and the character of the lesions of syphilis, if any

Syphilis of the pancreas in spite of Warthin's early opinion is excessively rare and usually clinically unrecognizable.

The Treatment of Syphilis of the Kidney

The treatment of the *renal lesions associated with early syphilis* is discussed in Chapter XIV

Late syphilis of the kidney is so difficult of absolute clinical identification that its frequency cannot be accurately estimated. It may occur in one of four forms (1) the lipoid nephrosis of Munk characterized by abundant albuminuria, doubly refractile lipoid cylindruria, anemia, edema (cf page 242) and absence of hypertension (2) contracted kidney' —chronic interstitial nephritis clinically indistinguishable from chronic nephritis in non-syphilitic patients (3) gumma of the kidney usually unrecognizable during life and (4) a hitherto undescribed peculiar form of nephritis found by Rich to occur in 6.5 per cent of 200 consecutive necropsies on syphilitic patients the clinical characteristics of which are not yet clear In addition amyloid nephritis may occur

Though the subject is yet in a very confused state it seems probable from what we now know that the prognosis of lipoid nephrosis and of the peculiar type of nephritis described by Rich is relatively favorable under appropriate therapy This statement is based on personal clinical experience with a small number of cases of lipoid nephrosis in which antisyphilitic treatment resulted in a complete disappearance of clinical symptoms and of urinary abnormalities and a return of renal function tests

to normal and on Rich's statement that from the pathologic standpoint there were marked evidences of healing of the lesions in the well treated cases in his series. On the other hand the prognosis in contracted kidney and amyloid nephritis is poor because of the degree of destruction of kidney parenchyma, irreplaceable by any method of treatment and poor in gumma of the kidney because of lack of ability to recognize and treat the lesion during life.

In any form of renal syphilis the type and intensity of antisyphilitic treatment will depend largely on information gained from studies of the degree of impairment of renal function. The arsenicals are safer than the heavy metals and of the two heavy metals, bismuth is safer than mercury.* Treatment should be started with an arsenical preferably neoarsphenamine or mapharsen, in small doses (0.05–0.1 gm. or 0.01–0.02 gm. respectively) each succeeding dose being cautiously increased by equally small increments if studies of the urine and of renal function show no signs of increased renal irritation. While such small doses are being used, treatment may be given at 4–5 day intervals which gradually lengthen to 7 days as the dose is increased. A dose of 0.3 gm. arsphenamine 0.6 gm. neoarsphenamine or 0.04 gm. mapharsen should not be exceeded. If the nephritis is syphilitic in origin one expects improvement, both clinical and laboratory within 2 months (10–12 injections of an arsenical preparation) of this sort of treatment. If improvement has occurred, heavy metal therapy may be started at the completion of the first course of the arsenical preparation employed. Since the heavy metals are more prone to produce renal damage in toxic doses than the arsenicals, and since the added liability to such damage, because of the already existing renal lesion, is not susceptible of exact estimation, the safest form of heavy metal therapy should be chosen i.e. the form least likely to cause cumulative toxic effects. This renders inadvisable the intramuscular use of insoluble salts of either bismuth or mercury. Instead one may employ a soluble bismuth salt, given intramuscularly, or mercury by inunction. Full doses of insoluble bismuth should not be given unless and until the evidences of renal disturbance disappear completely.

In this situation the arsenicals and the heavy metals should always be used in alternation, never concurrently. The total amount and duration of treatment will depend on the extent of the patient's improvement. If *urinary abnormalities clear up and impaired renal function improves*, treatment should be continued as in other forms of late syphilis, for a minimum of 15–24 months. If on the other hand improvement fails to occur and the kidney lesion appears to be progressive, it may be advisable to abandon treatment completely.

As in patients with non-syphilitic nephritis, a period of rest in bed under conditions of hospital control restriction of fluids in edematous patients and general symptomatic treatment are desirable. Diet as a factor in the control of nephritis seems to be becoming increasingly unimportant.

* As we have already said, there is no evidence that either the arsenicals or bismuth will produce renal damage when given in usual therapeutic doses to animals or human beings with normal kidneys.

The treatment of syphilis complicated by non syphilitic nephritis often presents difficult problems of judgment. Whether to treat such a patient at all in what fashion and for how long depend on a wide variety of factors When a syphilitic infection is complicated by acute glomerular nephritis it is wise to withhold all antisyphilitic treatment until the subsidence of the acute renal lesion. In patients with chronic nephritis without evidence of serious damage to renal function antisyphilitic treatment may be given the arsphenamines in usual dosage the heavy metals with caution If renal function is moderately or markedly impaired the decision as to whether to treat the patient at all will depend on the lesions of syphilis present if any and on the prognosis as to the nephritis Obviously nothing is gained by the antisyphilitic treatment of a patient whose only apparent evidence of syphilis is positive serologic tests, whose phthalein output is zero who has nitrogen retention and signs of impending uremia. On the contrary much can be accomplished in an individual with let us say aortic aneurysm a phthalein output of 20 per cent in 2 hours and slight or no nitrogen retention

One sees an occasional patient with urinary abnormalities suggesting chronic nephritis but with normal renal function tests in whom during the course of antisyphilitic treatment there is rapid downhill progress (within a year or two) to uremia and death. To what extent has the antisyphilitic treatment contributed to this disastrous outcome? This question is completely unanswerable with our present knowledge. We give it as our personal opinion that the combination of circumstances is coincidental rather than causative There is so far as we know no adequate evidence that either the arsenical preparation or bismuth *given in average therapeutic dosage* will cause renal damage even in an already diseased kidney (though as much cannot be said for mercury) except in association with other evidences of grave drug intoxication such as dermatitis blood dyscrasias, severe stomatitis or enteritis Certainly there is no evidence that modern syphilotherapeusis is responsible for the development of inflammatory or degenerative renal damage

The Treatment of Syphilis of the Testes and Bladder

Although syphilitic orchitis is a frequent post-mortem diagnosis (page 255) it occurs very seldom clinically and when it does must be differentiated from tuberculosis and cancer Syphilis of the bladder is sufficiently rare that we have never seen a case in either early or late syphilis. Once the diagnosis is established the treatment of these two complications is the same as for other types of late syphilis

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Chapter XX

THE TREATMENT OF OCULAR SYPHILIS

The proper management of ocular syphilis concerns equally the ophthalmologist and the syphilologist. Two problems must be faced the one sometimes, the other always. These are the preservation of the vital function of vision and the treatment of the systemic infection syphilis of which the ocular lesion is but a single manifestation. In many instances neither ophthalmologist nor syphilologist, working alone, is competent to deal successfully with these two major issues. The closest cooperation between the two is essential. The special knowledge and highly technical equipment of the one are required for accurate diagnosis for the observation and measurement of progress and for local therapeutic procedures. The more general knowledge of the other is essential properly to determine the possible ravages of syphilis elsewhere than in the eye to envisage its eradication or arrest, and to apply chemotherapeutic or other special measures of treatment, not only for the ocular lesion but also for the systemic disease. Much of the ophthalmologist's fear of arsenical drugs much of his scepticism as to the poor results of treatment in such lesions as interstitial keratitis and optic atrophy and many of the syphilologist's failures to preserve useful vision are directly traceable to the failure of each to appreciate the limitations of his own knowledge. Two physicians are better than one for the patient with syphilis of the eye.

The Effect of the Arsphenamines on the Normal or Diseased Eye

Superstitions persist in medicine as in religion. One of the most difficult to down is the ophthalmologist's fear of the possible deleterious effects of arsenical drugs on the eye. This is reflected in statements in the ophthalmologic literature (fortunately becoming less frequent) that arsphenamine and its derivatives should not be used in the treatment of ocular syphilis, and should be specially avoided in optic atrophy Not infrequently the syphilologist receives from his ophthalmologic confrère the direct request that such-and-such a patient be treated otherwise than with an arsphenamine. It is easy to trace the growth of this misapprehension which dates back to the use of atoxyl in the treatment of trypanosomiasis and its trial in syphilis. This drug and some of its later (and also discarded) derivatives did frequently produce a toxic amblyopia. The condemnation accorded to it carried over unjustly to arsphenamine was increased for a time by a misunderstanding of the mechanism of development of relapsing ocular lesions in inadequately treated patients with early syphilis and was in the process of gradually dying out when it was revived by the introduction of tryparsamide into the therapy of neurosyphilis.

That arsphenamine and its immediate derivatives (also including arsenoxide) have no deleterious effect on any of the structures of the eye has

been shown by many observers notably by Igersheimer and Zimmermann. The curious recent report of Skirball and Thurmon, that optic neuritis is *frequently* caused by arsphenamine, is at direct variance with the experience of all other observers. The whole subject has been ably reviewed by Zimmermann who classifies the direct and indirect effects of the arsphenamines on the eye as follows

1 *True toxic reactions*—The only true toxic arsphenamine reaction involving the normal eye occurs as conjunctival hyperemia. This is a common feature of the nitritoid crisis (see Chapter VII) in which it often precedes the cutaneous flushing. It may also occur as an isolated phenomenon analogous to fixed arsphenamine eruptions on the skin, appearing a few moments or several hours after each injection of the drug and usually accompanied by itching. Other structures of the eye, and in particular the retina and optic nerve are never damaged by the arsphenamines or mapharsen A secondary but very rare toxic ocular manifestation is superficial keratitis or corneal ulcer in association with a post-arsenical exfoliative dermatitis.

2 *Ocular therapeutic shock—the Jarisch Herxheimer reaction* —While *the normal eye is unaffected* the *diseased eye may be* seriously injured by a Herxheimer reaction following the initiation of arsenical therapy This may appear either as intensification of an already existing lesion as a flare-up in a quiescent lesion or as the unexpected appearance of an inflammatory process in structures previously apparently uninvolved

We have seen all these phenomena in syphilitic uveitis. The symptoms and signs of an iridocyclitis may temporarily be much worse for 24–48 hours following the first dose of arsphenamine. An old quiescent uveitis may be lighted up though this is uncommon A patient with secondary syphilis and apparently normal eyes may develop an acute uveitis within a day or two after starting treatment or in a patient with an already existing iritis but normal posterior chamber and fundus vitreous opacities chorioretinitis, or optic neuritis may appear to clear up with further treatment. The vitreous opacities due to syphilis are not to be confused with those not infrequently seen in the eyes of elderly individuals both syphilitic and non-syphilitic.

Zimmermann thinks the Herxheimer reaction is of clinical importance only in patients with optic neuritis or primary optic atrophy He cites a patient of his own and several others gathered from the literature in whom there was a violent inflammatory and hemorrhagic exacerbation in an already existing optic neuritis with permanent damage to vision following *the first injection of a large dose of arsphenamine.* He also mentions patients with primary optic atrophy in whom the failing vision was suddenly extinguished after the start of arsenical therapy He feels as does also Stokes that in such patients treatment should be started with a heavy metal or with very small doses of an arsenical to avoid therapeutic shock These reactions must however be very rare since we have seen only one example in optic neuritis and none in optic atrophy In either type of case we are not impressed with the necessity for long preparatory heavy metal

treatment and as will be seen, we take precisely the opposite position in optic atrophy In optic neuritis it is probably wise to concede to the danger to the extent of starting treatment with small doses of an arsenical (i.e., 0 1 gm. arsphenamine 0.3 gm. neoarsphenamine 0 030 gm. mapharsen) but increasing rapidly at 4–5 day intervals, to an average therapeutic dose.

In interstitial keratitis choroidal and retinal lesions, and in ophthalmoplegias, therapeutic shock is of little practical significance.

3 Ocular relapse —A frequent consequence of the *inadequate* arsenical therapy of early syphilis is relapse. Two forms are especially frequent iridorelapse and optic neuritis either occurring as an isolated phenomenon or as part of a neurorecurrence. The mechanism of these types of relapse is probably as follows substerilizing treatment with an arsenical drug may destroy all or most of the treponemes in the body except those in the eye or nervous system This sudden destruction of organisms by treatment prevents the tissue response and immune reactions called forth by the development of lesions and their spontaneous healing which occurs in untreated patients with early syphilis. The foci of organisms remaining in the nervous system or the eye are therefore at liberty to multiply as if they had been freshly introduced from without, and after an appropriate incubation period (which averages about two months) the inflammatory reaction has progressed to the point of causing an iridorecurrence. Ophthalmoplegias due to involvement of 3rd 4th or 6th nerves may also occur as neurorecurrences.

These lesions are not due to the arsenical drugs but to too little of them. They are cured by additional and more intensive arsenical treatment.

Tryparsamide in Syphilis of the Eye

This drug is of no value in the exudative and inflammatory lesions involving the external coats of the eye. Its only field of usefulness is in neurosyphilis. Here, however it may not be used with safety when there is involvement of the optic nerve or retina. Moore and Woods have shown that the incidence of symptoms of intolerance following its use is much greater in patients with pre-existing visual damage and under these circumstances there is grave risk of toxic amblyopia and permanent blindness (cf pp. 127–128)

The Treatment of Ocular Syphilis in General

There are no special procedures, ophthalmologic or otherwise to be adopted in the management of such lesions as chancre of the conjunctiva, gummatous episcleritis, gumma of the orbit chorioretinitis, or optic neuritis or neuroretinitis (except, in the last named avoidance of therapeutic shock, as noted above) The treatment of these conditions is the treatment of the appropriate stage of syphilitic infection early or late. Five situations involving the eye however call for special management These are (1) involvement of the uveal tract in early or late syphilis (2) chronic relapsing chorioretinitis or neuroretinitis—drug resistant ocular syphilis (3) the optic atrophies (4) interstitial keratitis of congenital

syphilis and (5) the question of ocular operations in patients with syphilis. We shall discuss each of these on the basis of our own considerable material, studied in conjunction with the staff of the Wilmer Ophthalmological Institute

The Treatment of Iritis, Uveitis, and Kerato-Iritis of Early and Late Syphilis

Moore and Gieske have studied the outcome of treatment in 249 patients with syphilitic involvement of the iris. The following paragraphs are based on a consideration of their patients and of Zimmermann's excellent survey of 190 similar cases The association of lesions elsewhere in the body with iritis occurring as a part of early relapsing or late syphilis is shown in Table 67 which emphasizes the necessity for consideration of

TABLE 67
THE ASSOCIATION OF INVOLVEMENT OF THE IRIS WITH OTHER LESIONS OF SYPHILIS (Moore and Gieske)

Type of iritis	Total patients	Percentage of patients with associated lesions of early or late syphilis					
		No associated lesion	Early secondary syphilis	Relapsing mucocutaneous lesions	Neurosyphilis	Cardiovascular syphilis	Benign late skin or bone lesions
Early	110	4 5	95 5	—	0 9	—	—
Relapsing	27	74 0	—	11 2	14 8	—	—
Late	108	50 0	—	—	12 0	14 8	31 4

the patient as a whole in planning therapy The frequent association of irido- and neurorelapse is shown in the table Thus in uveitis accompanying early or relapsing secondary syphilis the general treatment problem is that of early syphilis. Control of infectiousness and the radical "cure" of the disease are the aims in view In patients with late involvement of the iris or uveal tract the major general treatment problem may be not the management of the ocular lesion but that of an associated vascular or neurosyphilis. Thus in any patient with ocular syphilis treatment should never be started until the patient has had a complete general as well as a special ophthalmologic examination in order properly to evaluate the problem with which the therapist is faced

Furthermore, and especially in early relapsing and late syphilis isolated involvement of the iris is the exception rather than the rule. Other and perhaps more important ocular structures may be damaged In our own series of patients the association of other ocular lesions with syphilitic iritis occurred as indicated in Table 68 The frequent association of optic neuritis or neuroretinitis in early and relapsing iritides and of kerato-iritis in late syphilis deserves special mention

TABLE 68

OTHER OCULAR LESIONS ASSOCIATED WITH SYPHILITIC IRITIS
(Moore and Gieske)

Type of iritis	Total patients	Percentage of patients with associated involvement of					
		No other ocular lesion	Uveal tract	Cornea	Lens	Retina	Optic nerve
Early	111	49 5	16 2	17 1	—	—	15 3
Relapsing	29	34 5	20 6	37 9	3 4	3 4	24 1
Late	109	22 0	9 1	66 0	4 5	6 4	8 2

Local ophthalmologic treatment —In order to prevent adhesions between iris and lens (posterior synechiae) or to break up those which have already formed, atropine (1 per cent solution) should be instilled into the affected eye three times daily until all signs of acute inflammation have subsided. *The pupil should be dilated as widely as possible.* Subconjunctival injection of atropine and cocaine sometimes gives dilatation of the pupil in eyes in which the synechiae are too dense to yield to conjunctival instillation of the drug. If the iris is tightly bound down to the lens so that all communication between the anterior and posterior chambers is abolished secondary glaucoma may result. The intra-ocular tension should therefore be carefully watched if it begins to rise atropine should be discontinued and operative interference considered Secondary glaucoma is an uncommon complication of early iritis (only twice in our 140 patients with early and relapsing iritis) but 14 of our 109 patients with late iritis developed this sequel, requiring operation in almost every instance and often leading to permanent visual damage

The eyes should be protected from light with dark glasses. With the more severe forms especially those with other ocular lesions (common in iritis as a relapse phenomenon) rest in bed is desirable. The oral administration of sodium salicylate in doses up to 6–7 gms. a day is an accepted therapeutic procedure in all forms of iritis, including that due to syphilis and in addition to its healing effect on the lesion, it is the most valuable means of controlling pain.

Attempts at local introduction of antisyphilitic drugs (for example subconjunctival injections of soluble mercurial salts) are undesirable, of no value and should not be employed.

The antisyphilitic treatment of iritis —The treatment of iritis accompanying early or relapsing secondary syphilis is that of early syphilis (Chapter XIII) Treatment should be started with an arsenical drug there is no point in preliminary heavy metal treatment to avoid therapeutic shock, which is not important in iritis. The ocular lesion usually heals promptly without permanent residual damage but *treatment must be continuously prolonged for a full year after serologic tests have become and*

introduction of the arsphenamines did not materially improve the situation. Patients treated with an intravenous arsphenamine bismuth, mercury and the iodides in any combination and for any length of time apparently became blind about as rapidly as in some cases more so than, untreated patients. Experiences of this sort have led most ophthalmologists and syphilologists to an attitude of complete pessimism as to the possibility of preservation of vision. Recent studies, particularly from the Johns Hopkins clinic indicate however that this pessimism is not wholly justified and that not infrequently useful vision may be preserved by proper treatment The following paragraphs are based on our own experience and on a review of the important literature from which we quote extensively

When a patient is completely blind and the fibres of the optic nerve are completely degenerated it is obvious that vision cannot be restored by any form of treatment. Dead nerve fibres cannot be replaced by living ones If any form of treatment is to be successful it must aim not at the replacement of dead tissue but at the arrest of the degenerative process The ultimate success or failure of treatment depends, therefore on whether or not it is started while sufficient functioning nerve fibres remain so that if they can be preserved, useful vision is retained. How to determine what proportion of fibres in the nerve have already been destroyed is sometimes difficult and perhaps best measured not by the degree of pallor of the disc or of constriction of visual fields but by central visual acuity Our own studies, and those of others, have established as a rough working formula the following if central visual acuity in the better eye is 20/60 or better there is about a 50 per cent chance of retaining useful vision with vision in the better eye between 10/200 and 20/60 the prognosis is bad and if less than this blindness is almost inevitable in spite of any treatment

Certain types of optic atrophy appear in which the prognosis is relatively good There are (1) when the atrophic process is still apparently unilateral and when visual acuity and fields in the better eye are still normal or nearly so (2) a small group of patients in whom the visual field defect includes a central scotoma with slight or moderate peripheral constriction. The first of these types is by far the most favorable with adequate treatment the appearance of atrophy in the uninvolved eye may often be permanently prevented In our own material involvement of the normal eye was prevented in 7 of 10 cases

When there is simultaneous bilateral loss of visual acuity and constriction of form and color fields, the prognosis is relatively bad especially if early downhill progress is rapid It is quite apparent however that these finer distinctions fade into comparative insignificance beside the factors of early diagnosis and the prompt institution of treatment Delay and procrastination are fatal to the preservation of vision

The treatment of primary optic atrophy Methods Routine antisyphilitic treatment —While as will be shown later intensive routine antisyphilitic treatment retards the progress and prevents the development of blindness in a small number of cases its use introduces

TABLE 63

OTHER OCULAR LESIONS ASSOCIATED WITH SYPHILITIC IRITIS
(Moore and Gleske)

Type of iritis	Total patients	Percentage of patients with associated involvement of					
		No other ocular lesion	Uveal tract	Cornea	Lens	Retina	Optic nerve
Early	111	49.5	16.2	17.1	—	—	15.3
Relapsing	29	34.5	20.6	37.9	3.4	3.4	24.1
Late	109	22.0	9.1	66.0	4.5	6.4	8.2

Local ophthalmologic treatment.—In order to prevent adhesions between iris and lens (posterior synechiae) or to break up those which have already formed, atropine (1 per cent solution) should be instilled into the affected eye three times daily until all signs of acute inflammation have subsided. The pupil should be dilated as widely as possible. Subconjunctival injection of atropine and cocaine sometimes gives dilatation of the pupil in eyes in which the synechiae are too dense to yield to conjunctival instillation of the drug. If the iris is tightly bound down to the lens, so that all communication between the anterior and posterior chambers is abolished, secondary glaucoma may result. The intra-ocular tension should therefore be carefully watched. If it begins to rise, atropine should be discontinued and operative interference considered. Secondary glaucoma is an uncommon complication of early iritis (only twice in our 140 patients with early and relapsing iritis), but 14 of our 109 patients with late iritis developed this sequel, requiring operation in almost every instance and *often leading to permanent visual damage.*

The eyes should be protected from light with dark glasses. With the more severe forms, especially those with other ocular lesions (common in iritis as a relapse phenomenon), rest in bed is desirable. The oral administration of sodium salicylate, in doses up to 6–7 gms. a day, is an accepted therapeutic procedure in all forms of iritis, including that due to syphilis, and in addition to its healing effect on the lesion, it is the most valuable means of controlling pain.

Attempts at local introduction of antisyphilitic drugs (for example, subconjunctival injections of soluble mercurial salts) are undesirable, of no value, and should not be employed.

The antisyphilitic treatment of iritis.—The treatment of iritis accompanying early or relapsing secondary syphilis is that of early syphilis (Chapter XIII). Treatment should be started with an arsenical drug; there is no point in preliminary heavy metal treatment to avoid therapeutic shock, which is not important in iritis. The ocular lesion usually heals promptly without permanent residual damage, but *treatment must be continuously prolonged for a full year after serologic tests have become and*

remained permanently negative It is worse than useless to treat the patient only until the eye is well or the blood serologic test negative Late iritis should be managed as late syphilis, i.e. treatment may be less intense in accordance with the principles discussed in Chapters XV and XVI The presence of complicating cardiovascular or neurosyphilis may however modify the treatment situation completely

The results of treatment of iritis —The results expressed in terms of the outcome as to useful vision obtained in our own patients by the application of these treatment methods are shown in Table 69 At any stage of syphilis iritis and its complications are potentially dangerous to vision. The danger is least in the early grows progressively greater in the recurrent, and is greatest in the late iritides. Permanent visual damage may be due to exudate on the anterior surface of the lens from contact with the inflamed iris to its late sequel complicated cataract or to such other complications as *keratitis with residual* corneal opacities neuroretinitis or chorioretinitis or to secondary glaucoma. In our series of patients with late iritis, many of the poor results were directly due to delay in arriving at a correct etiologic diagnosis Thirty-four per cent of our patients had had the ocular lesion for more than one year before a correct diagnosis was reached.

TABLE 69

THE ULTIMATE OUTCOME OF THE EYE LESION IN SYPHILITIC IRITIS
(Moore and Gieske)

Type of iritis	Total patients with known *outcome*	Percentage of patients with vision in affected eye			
		Blind	Poor (less than useful vision)	Fair (moderate visual impairment, one or both eyes)	Good (practically no residual damage)
Early	69	—	10.1	2.2	87.6
Relapsing	22	9.0	13.6	—	77.2
Late	79	12.6	21.5	7.6	58.2

Repeated relapses of iritis are comparatively uncommon.

Chronic Relapsing Chorioretinitis or Neuroretinitis

We have seen three patients, and Zimmermann reports another in whom there were frequent ocular relapses involving the choroid, retina or optic nerve occurring in the midst of treatment. In all these cases the relapse appeared while the patient was on bismuth or mercury cleared up promptly on the renewal of an arsphenamine and reappeared as soon as the arsenical was discontinued in favor of the heavy metals One of our patients had five such relapses Zimmermann's patient had six. These unfortunate individuals must be classified as examples of drug resistance

(Chapter XIII) Treatment should be altered (a) to include very prolonged courses of arsphenamine (12–20 weekly injections), or (b) by a change in the arsenical product (e.g silver arsphenamine in place of arsphenamine) or (c) by the use of fever therapy or by all three.

Optic Atrophy

The secondary syphilitic optic atrophies are the end result of neuroretinitis or optic neuritis or are associated with extensive inflammatory lesions of choroid and retina. They are relatively uninfluenced by treatment and call for no special measures.

Retrobulbar neuritis (involvement of the papillo-macular bundle with central scotoma) as an entity due to syphilis is rarely observed and is probably secondary to involvement of the superficial and exposed portions of the optic tract in syphilitic basilar meningitis Recent studies (Sloan and Woods) however have shown that a central scotoma occurs much more often in primary optic atrophy than was formerly supposed.

Primary optic atrophy Its pathogenesis course and prognosis —Moore and Woods have recently critically reviewed the literature on the newer theories of the pathogenesis of primary optic atrophy Those advanced so far are that it may be due to (1) the virus of lymphogranuloma inguinale (2) vasoconstriction within the optic nerve with consequent nutritional disturbances leading to optic atrophy (3) a disturbance of the interrelationship between intraocular tension and the retinal arterial systolic and diastolic blood pressure, (4) an adhesive chiasmal arachnoiditis, (5) a combination of neurosyphilis and nutritional deficiency Moore and Woods conclude that while an occasional case of syphilitic optic atrophy may be due to an adhesive optochiasmal arachnoiditis it seems most probable that the pathogenesis of syphilitic primary optic atrophy so frequently associated with tabes dorsalis is in most instances identical with that of tabes. That, in addition to syphilis vitamin deficiency may play an important part in the production of tabes either with or without optic atrophy is suggested by the experimental studies of Mellanby Wintrobe Zimmermann and Burack and others and the clinical observations of D G F Moore and of Sydenstricker and his associates. These interesting theories, however are in need of further elaboration before they can be accepted.

The course of untreated syphilitic optic atrophy invariably leads to complete blindness since although it may begin unilaterally the second eye always becomes involved. In a series of 249 cases of untreated optic atrophy 117 from the Wills Hospital and 132 from the Johns Hopkins clinic complete bilateral blindness (visual acuity of 10/200 or less in the better eye) occurred within 3 years from the onset of symptoms in 90 per cent of cases. In rare instances progression was slower but all were blind by the end of the ninth year Temporary or spontaneous remissions seldom if ever occur

From the standpoint of vision the treatment of primary optic atrophy in the pre-arsphenamine era was unsatisfactory Blindness resulted as rapidly as if nothing had been done. Until recently it was thought that the

introduction of the arsphenamines did not materially improve the situation. Patients treated with an intravenous arsphenamine bismuth mercury and the iodides in any combination and for any length of time apparently became blind about as rapidly as in some cases more so than untreated patients Experiences of this sort have led most ophthalmologists and syphilologists to an attitude of complete pessimism as to the possibility of preservation of vision. Recent studies particularly from the Johns Hopkins clinic indicate however that this pessimism is not wholly justified and that not infrequently useful vision may be preserved by proper treatment. The following paragraphs are based on our own experience and on a review of the important literature, from which we quote extensively

When a patient is completely blind and the fibres of the optic nerve are completely degenerated it is obvious that vision cannot be restored by any form of treatment. Dead nerve fibres cannot be replaced by living ones. If any form of treatment is to be successful it must aim not at the replacement of dead tissue but at the arrest of the degenerative process The ultimate success or failure of treatment depends therefore on whether or not it is started while sufficient functioning nerve fibres remain so that if they can be preserved useful vision is retained. How to determine what proportion of fibres in the nerve have already been destroyed is sometimes difficult and perhaps best measured not by the degree of pallor of the disc, or of constriction of visual fields but by central visual acuity Our own studies and those of others have established as a rough working formula the following if central visual acuity in the better eye is 20/60 or better there is about a 50 per cent chance of retaining useful vision with vision in the better eye between 10/200 and 20/60 the prognosis is bad and if less than this blindness is almost inevitable in spite of any treatment.

Certain types of optic atrophy appear in which the prognosis is relatively good These are (1) when the atrophic process is still apparently unilateral and when visual acuity and fields in the better eye are still normal or nearly so (2) a small group of patients in whom the visual field defect includes a central scotoma with slight or moderate peripheral constriction. The first of these types is by far the most favorable with adequate treatment, the appearance of atrophy in the uninvolved eye may often be permanently prevented In our own material involvement of the normal eye was prevented in 7 of 10 cases

When there is simultaneous bilateral loss of visual acuity and constriction of form and color fields the prognosis is relatively bad especially if early downhill progress is rapid It is quite apparent however that these finer distinctions fade into comparative insignificance beside the factors of *early diagnosis and the prompt institution of treatment.* Delay and procrastination are fatal to the preservation of vision.

The treatment of primary optic atrophy Methods Routine antisyphilitic treatment —While as will be shown later intensive routine antisyphilitic treatment retards the progress and prevents the development of blindness in a small number of cases its use introduces

the fatal element of delay During the time consumed by these efforts, further degeneration of the diseased nerve, to the point that other types of treatment are useless, may occur When it becomes obvious to the therapist that more drastic measures are necessary it may be too late and a hopeful situation may be converted into a hopeless one.

Tryparsamide —Although tryparsamide is not absolutely contraindicated in the treatment of primary optic atrophy *the incidence of toxic amblyopia following its use in patients with previously diseased optic nerves is ten times greater than in those with normal eyes* For practical purposes therefore, its use entails a risk which the therapist can well avoid by employing less hazardous and better proved methods.

Local treatment of the optic nerve —Vasodilator drugs carotid sympathectomy retrobulbar injections of atropine, and cyclodialysis have been used in the treatment of optic atrophy on the assumption that the disease process was due (1) to syphilitic changes in the blood vessels of the nerve or (2) to a disturbance of the normal relationship between the systemic and retinal blood pressure and the intraocular tension. There is no evidence that either of these factors is responsible for syphilitic optic atrophy and it is not surprising therefore that treatment aimed at correcting them has proved unbeneficial.

Operations on the optic nerve —On the assumption that some cases of syphilitic optic atrophy may be due to an adhesive optochiasmal arachnoiditis as a result of a previous basilar meningitis, several observers, particularly Bollack, David and Puech, and in this country Hausman and Vail, have attempted surgical removal of the thickened arachnoid from around the optic chiasm. In the cases in which the diagnosis was confirmed at operation removal of the adhesions resulted in improvement of vision or arrest of blindness in approximately 50 per cent. Unfortunately the post-operative follow-up of these patients so far reported has not exceeded 7 months (except in one case observed for 2 years after operation by Hausman) Dandy has performed the operation for us in 3 patients in whom atrophy progressed in spite of other treatment methods but in none was any evidence of adhesive arachnoiditis found and no benefit resulted from the operation. Nevertheless we believe that neurosurgical exploration of the chiasmatic area is justifiable as a last resort, if visual failure progresses in spite of fever and subdural therapy

Subdural treatment —The technique of this method of treatment by either intraspinal or intracisternal routes is discussed in Chapter XXIII The fact that successful results have been reported after the subdural injection of such various substances as neoarsphenamine dissolved in spinal fluid, arsphenaminized serum mercurialized serum and air indicates that the sterile meningitis induced rather than the actual medicament is the responsible factor

Our personal preference in the treatment of optic atrophy is for arsphenaminized serum introduced intracisternally the patient lying flat on his face for 3–4 hours after treatment. This is calculated to place the serum in intimate and concentrated contact with the diseased areas in and anterior to the optic chiasm Vranesic suggests that much the same result

may be obtained by giving the serum intraspinally and by standing the patient on his head afterwards. This is accomplished as follows Immediately after treatment the patient is laid face down across a bed. His hips are at the extreme edge his weight supported by his thighs and legs on the bed and by his crossed forearms on pillows on the floor his head cushioned by his arms. He is left in this position almost literally standing on his head for 15 to 25 minutes then he is put to bed with the foot of the bed elevated 12–18 inches, for 10 to 15 hours. Under these circumstances the heavy serum (specific gravity 1 027–1 030) gravitates through the light spinal fluid (specific gravity 0 99–1 000) to the most dependent portion. We have used Vrančić's method in patients in whom cisternal puncture was unsuccessful or undesirable (e.g in women who may object to shaving the occipital region) By either route the same restrictions apply as to subdural treatment for any other type of neurosyphilis (1) remove about 5 cc. more spinal fluid than the volume of serum to be introduced (2) never give more than 20 cc. of serum at a dose (better to start with 5–6 cc. and increase gradually to 12–15 cc) (3) an interval of two full weeks between treatments (4) no more than 6 treatments in a series. These precautions rob the method of its worst danger—irritation of the cord and subsequent myelitis.

There is some danger of therapeutic shock in starting treatment with combined intravenous and subdural treatment. In about 10 per cent of patients it carries the risk of sudden blindness especially in patients with far advanced lesions. In our own experience however this is distinctly uncommon and Schacherl on the basis of a very large experience thinks the danger does not exist. In any case it is a risk which must be accepted if this method of therapy is indicated. Without adequate treatment the inevitable result is blindness even if treatment hastens the process in a few patients it is justified by the favorable results secured in others.

The method is particularly valuable in patients with associated cardiovascular syphilis. Here because of the danger of fever therapy or intravenous arsenical treatment, heterologous arsphenaminized serum (i e serum from another treated patient) may be used supplemented by the heavy metals.

Fever therapy —During the past ten years an increasing number of reports on the results of the treatment of optic atrophy with fever have appeared in the literature In the majority of these fever was produced by malaria inoculata. Only a few patients have been treated with mechanically induced fever and these have not been followed long enough to permit any accurate evaluation of the result. The method of choice is therefore malaria. All observers are agreed that in an occasional patient the vision may be rapidly extinguished during the first few paroxysms of fever This risk is not as great as after subdural treatment, and we have never seen an example. However malaria does carry with it a small risk to life not involved in subdural treatment. Fever therapy is especially of value in optic atrophy associated with paresis or taboparesis and in this situation is the method of choice for the initiation of treatment but when employed it must be as will be shown later followed by appropriate after treatment.

Treatment of primary optic atrophy Results —The long-term evaluation of the results of treatment of optic atrophy by Moore and Woods and their associates makes their report (1938) the most comprehensive of any so far to appear Their cases, followed from 6 to 19 years after the onset of symptoms may be divided into six groups as follows

1) 182 patients who received no treatment at any time.

2) 30 patients who received only inadequate routine treatment, arbitrarily defined as less than 10 injections of a trivalent arsenical and 10 injections of a heavy metal or the equivalent thereof

3) 46 patients who received adequate routine treatment i.e more than 10 injections each of an arsenical and a heavy metal.

4) 31 patients whose treatment was initiated with one or more subdural intraspinal or intracisternal injections of arsphenaminized serum by the Swift Ellis technique, this form of treatment being either accompanied or followed by routine treatment.

5) 26 patients whose treatment was initiated by induced malaria followed by routine treatment.

6) And among these totals 27 patients treated by a combination of two or more of these systems.

Their experience indicates clearly (1) that the trivalent arsenical drugs and the heavy metals do not possess any direct toxic affinity for the optic nerve (as do the pentavalent arsenicals e.g tryparsamide) and that blindness is not precipitated by standard methods of use (2) that in about 10 per cent of the patients treated the subdural method does carry a risk of sudden progression of the atrophic process, even to the point of blindness (3) that if malaria exercises a similar deleterious effect (as is reported by several observers abroad) this must be an uncommon event, since they did not observe an instance in some 60 patients so far treated.*

With few exceptions, they did not use tryparsamide in the treatment of primary optic atrophy because of the previously reported opinion that this drug is contra-indicated in the presence of pre-existing damage to the nerve.

The Results of Treatment

The outcome of treatment is presented as a series of curves in Fig. 44, in which the abscissa represents the cumulative percentage probability of blindness and the ordinate the time of observation in years dating from the onset of symptoms

The figure indicates that with inadequate routine treatment all patients probably become blind in approximately the same time period as when no treatment is given. With adequate routine treatment, the progress toward blindness seems to be appreciably slowed. Whereas untreated patients are all blind by the end of the seventh year only 69 per cent of those given adequate routine treatment are blind by the ninth year If the considerations given by Moore and his associates as to selection of material applied uniformly that "rapid progressors" may fall in the untreated group and

* The majority of these malaria-treated patients were not included in the 1938 study because of inadequate length of post-treatment observation.

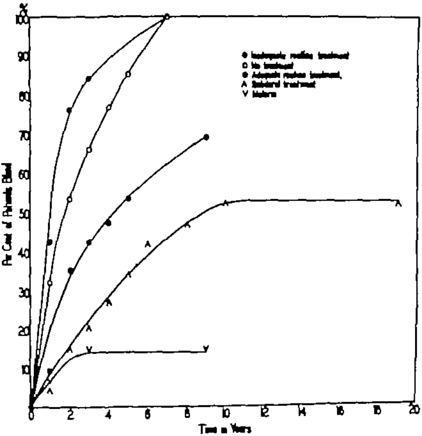


FIG. 44.—Showing the per cent of patients with syphilitic primary optic atrophy who became blind within the specified time period after different treatment methods (or when untreated) "Not blind" includes all those who retained central visual acuity in the better eye of 10/200 or more.

"slow progressors in the treated groups the difference between no treat ment and adequate routine treatment would probably be insignificant. A study of individual records suggests however that not only may adequate routine treatment delay the onset of blindness in a fair proportion of cases but also and *particularly if treatment is begun very early* it may occasionally arrest the atrophic process entirely

There can be no statistical doubt as to the beneficial effect of subdural treatment or malaria. In the case of subdural treatment the data indicate that by the tenth year only 53 per cent of patients are blind and that if by this time the patient is still not blind the process is probably permanently arrested. This satisfactory result is observed in spite of the fact that in four of the forty-one cases represented in this curve blindness was appar ently precipitated by treatment. These findings are in agreement with those of other observers.

With induced malaria the results are apparently even better although the number of cases represented is too small for certainty Within three

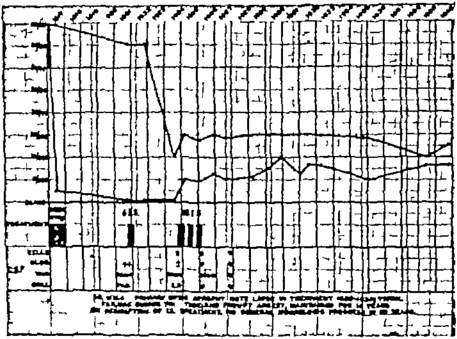


FIG. 45.—Showing (1) the failure of routine treatment (1917) to prevent rapid visual loss in one eye and slow progression of atrophy in the other (2) the failure of inadequate subdural treatment (1921) to prevent still further progression (3) the effect of adequate subdural treatment (1924-1926) in preventing additional visual loss (4) the preservation of useful vision over a 17 year period (1924-1940)

years 14.6 per cent of the patients treated are blind but thereafter the curve is completely flat. Although their cases have not been followed so carefully or for so long a period numerous other observers report results closely paralleling those of Moore and Woods. In a compilation from the literature of 259 cases treated by the subdural method (Table 70) 153

TABLE 70

RESULTS OF SUBDURAL TREATMENT OF OPTIC ATROPHY

Total patients treated	Percentage of patients	
	Improved or stationary	Unimproved or worse
259	58	42

(58.2 per cent) were slightly improved or stationary while among 343 patients treated with induced malaria (Table 71) arrest or improvement was observed in 187 (54.5 per cent) 123 of whom had been followed for more than one year after treatment (Moore and Woods)

TABLE 71

RESULTS OF FEVER THERAPY IN OPTIC ATROPHY

Total patients treated	Percentage of patients	
	Improved or stationary	Unimproved or worse
343	54	46

A study of individual case records confirms the fact that the progress of primary optic atrophy may be completely arrested by the use of either subdural treatment or malaria, more often by the latter Both of these procedures however must be followed by at least 2 years of intensive routine antisyphilitic treatment with the trivalent arsenicals and bismuth.

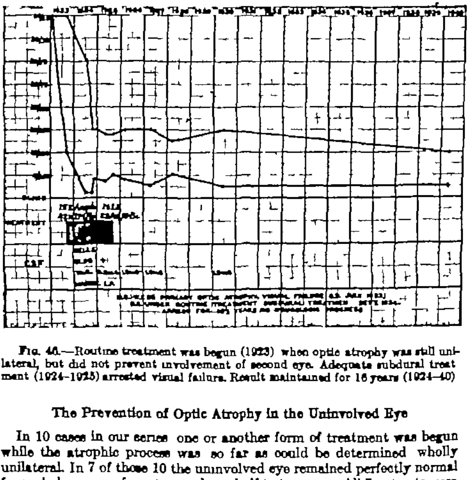


FIG. 46.—Routine treatment was begun (1923) when optic atrophy was still unilateral, but did not prevent involvement of second eye. Adequate subdural treatment (1924–1925) arrested visual failure. Result maintained for 16 years (1924–40)

The Prevention of Optic Atrophy in the Uninvolved Eye

In 10 cases in our series one or another form of treatment was begun while the atrophic process was so far as could be determined wholly unilateral. In 7 of those 10 the uninvolved eye remained perfectly normal for periods ranging from two and one-half to ten years. All 7 patients were treated with subdural therapy malaria, or both. Two of the three in

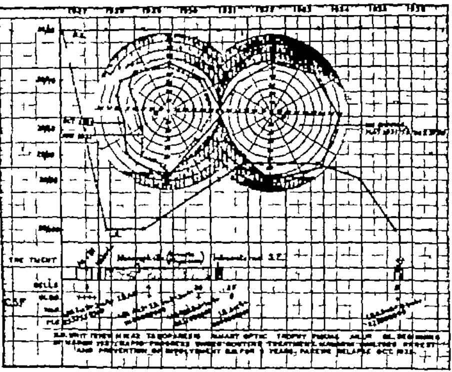


FIG. 47

whom visual failure occurred in the previously uninvolved eye received routine treatment only

Ophthalmologic control of treatment for optic atrophy Local treatment —Before during and after treatment, a patient with primary optic atrophy should be under rigid ophthalmologic control Measurements of the progress of treatment depend on accurate records of visual acuity and visual fields. These data should be available before treatment is started and during its course should be obtained at least as frequently as every three months. Local ophthalmologic treatment of any sort by subconjunctival injection or otherwise, is of absolutely no value.

General considerations of the treatment of primary optic atrophy —It need hardly be emphasized that neither subdural treatment nor fever therapy are methods to be used by the inexperienced tyro. Both are highly technical and specialized procedures involving some risk to the patient and neither should be undertaken without expert guidance In Table 72 are summarized briefly the indications for each of these treat ment methods and suggested outlines for their use.

Interstitial Keratitis

Interstitial keratitis is the commonest lesion of late congenital syphilis. Approximately half of all patients with late congenital syphilis seek aid

TABLE 72

SUGGESTED OUTLINE OF MANAGEMENT FOR SYPHILITIC PRIMARY OPTIC ATROPHY

	Method of treatment	
	Subdural	**Fever**
Indications	1 Any form of primary optic atrophy except that associated with paresis or taboparesis. 2 To follow fever therapy in patients in whom visual failure progresses in spite of fever	In optic atrophy associated with paresis or taboparesis.
Method of choice	1 In all cases except those associated with C V syphilis, homologous arsphenaminized serum. 2. With associated C.V syphilis, heterologous arsphenaminized serum. (No intravenous arsphenamine.)	Malaria
Prognosis	Even chance of arrest if vision in better eye is 20/40 or more.	About 60 per cent chance of arrest if vision in better eye is 20/40 or more.

Course	Weeks	Suggested Treatment	Course	Weeks	Suggested Treatment
I	1,3,5,7 9, 11 (6 treatments) 2 4,6,8, 10, 12	Neo (0 6–0 75 gm) or silver arsphenamine (0.3 gm.) followed same or next day by 6–15 cc. arsphenaminized serum subdurally Neo or silver arsphenamine I V No subdural treatment.	I II	1–6 7–12	Malaria Tonic course of neoarsphenamine (6×0.3–0 6 gm.)
II	13–20	8 × bismuth 0.2 gm. I M weekly K.I gms. 6–12 daily	III	13–20	8×bismuth. K.I
III	21–32	Repeat Course I	IV	21–30	10 × silver arsphenamine 0.3 gm
IV	33–44	12 × bismuth 0.2 K.I			
V and after		1 If visual failure progresses try fever 2 If visual failure is arrested for 3–4 months, continue alternating courses of I V and I.M therapy for at least 2 years. 3 Even if patient becomes completely blind, continue treatment for sake of other possible damage from neurosyphilis. Tryparsamide possible now but not before.	V and after		1 If arrest of visual failure, continue alternating courses I V and I.M for at least 2 years. 2. If visual failure progresses, try subdural treatment. 3 No tryparsamide unless patient becomes completely blind.
Control of treatment		1 Frequent ophthalmologic survey—every 3 months 2. Examine cerebrospinal fluid at least every 6 months			

because of it. Untreated interstitial keratitis involves both eyes, either simultaneously or in sequence in the majority of instances. It is generally thought to be one of the most resistant to treatment of all syphilitic lesions. The following discussion of treatment is based largely on a survey of the Johns Hopkins material by Robinson and on the studies of Carvill and Derby Lazarescu Lennarson and Jeans the C C G and particularly the excellent study by Klauder and Vandoren.

Local treatment —As in uveitis, atropine, dionine dark glasses and avoidance of ocular work are essential. Other forms of local treatment, such as yellow oxide of mercury ointment and subconjunctival injections of soluble mercurials are useless and unnecessary Roentgen therapy will be discussed subsequently Salicylates, as in iritis, are of some value. The local application of 2 per cent quinine bisulphate ointment, as advised by Selinger is in our experience of no value.

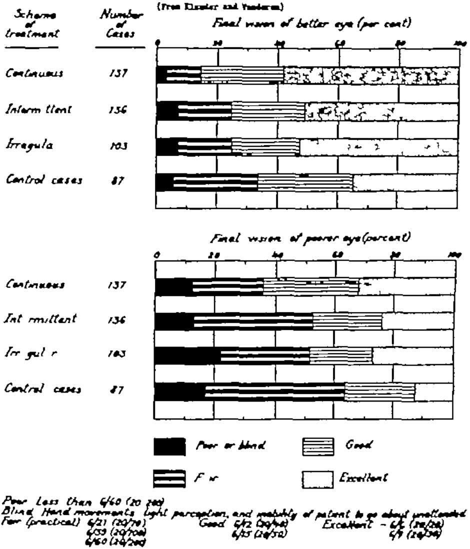
General treatment —The success of antisyphilitic treatment depends partly on early diagnosis and the prompt institution of therapy Interstitial keratitis appears most frequently between the ages of 7 and 18 years in females and from the 5th to the 20th year in males, but unfortunately is often not immediately recognized. In the Johns Hopkins material (182 cases studied by Robinson), 39 patients had had this complication for more than one year (17 of them for more than 10 years!) before the lesion was recognized as syphilitic in the meanwhile had consulted numerous agencies for relief including opticians, optometrists general practitioners and in some instances, even ophthalmologists and had received no antisyphilitic treatment whatever! The outcome in these patients was usually disastrous, in the form of dense and irremediable corneal scars. In addition, as will be shown later the early recognition and treatment of unilateral interstitial keratitis often prevents involvement and possible visual impairment of the second eye.

Our plan of treatment for patients with interstitial keratitis consists of courses of an arsphenamine alternating with courses of bismuth. Old arsphenamine (606) is usually employed for its superior therapeutic effect, and the average dosage is larger than in patients with less serious or less resistant lesions. Children tolerate without serious reaction a dosage level of 0 1 gram per 25 pounds of body weight. Many failures are attributable to over-cautious treatment with small doses (0.3–0 6 gm) of neoarsphenamine. Potassium iodide, according to Klauder and Vandoren should never be given. A series of 15–20 intravenous injections of a soluble mercurial salt (succinimide 0 01 gm.) given daily except on the day of arsphenamine injection, or the biweekly injection of a soluble bismuth preparation for the first 4–6 weeks, is of added value. As shown by Klauder and Vandoren (Fig. 48) treatment should be continuous rather than intermittent or irregular and should consist of a minimum of 30 injections of an arsenical preparation and 40–60 of bismuth subsalicylate before rest periods are permitted. Not only does this minimize the possibility of relapse but the end results as far as vision is concerned are appreciably better Treatment should be continued for a minimum period of 2 years, regardless of serologic progress. Seroresistance is the rule in late congenital syphilis and no

FIG 48

FINAL VISUAL ACUITY OF PATIENTS WITH INTERSTITIAL KERATITIS FOLLOWING DIFFERENT PLANS OF TREATMENT COMPARED WITH VISUAL ACUITY OF CONTROL GROUP

(From Klauder and Vandoren)



amount of treatment may be successful in reversing the test to negative and maintaining it so

If the inflammatory process is acute (i.e., of less than 3 months duration, and before the formation of dense corneal scars) improvement is usually immediate though slow Occasionally there is a definite Herxheimer flare-up the inflammation in the affected eye becoming temporarily

worse. This may be disregarded as of no practical importance. Complete resolution of the active inflammatory process usually occurs in 6–16 weeks leaving residual corneal opacities of greater or less extent. Even these opacities may resolve further and eventually disappear after several months of continued treatment.

Interstitial keratitis resistant to routine treatment.—Frequently a resistant case is encountered in which this régime of alternating courses of arsphenamine and bismuth fails to bring about improvement. Under these circumstances fever therapy should be instituted at once if possible. Although we have had experience with only a few cases, excellent results in treatment-resistant patients following malaria have been reported by Ambler and Van Cleve Anderson and Wilson and Klauder and Vandoren. If fever therapy is not available, or is contra-indicated routine treatment must be intensified or altered. It is wise under these circumstances to change the drug employed For example, we have observed some patients in whom the lesion grew worse under weekly injections of arsphenamine but in whom prompt healing was brought about when silver arsphenamine was given twice weekly and combined with simultaneous intramuscular injections of bismuth and larger doses of potassium iodide. In addition one of us (Kemp) has supplemented routine treatment in resistant cases unable to obtain malarial fever with the injection of non-specific proteins (milk, bacterial proteins) While the results were not as satisfactory as those reported following malaria, they appeared appreciably better than following routine treatment alone. Klauder and Vandoren report similar experiences.

The results of treatment of interstitial keratitis.—Carvill and Derby's and Klauder and Vandoren s series of patients are the largest, best treated and most thoroughly studied in the literature In Table 73 the results of the former investigators are summarised in terms of visual acuity in the better eye in treated as compared with untreated patients.

TABLE 73

VISION IN THE BETTER EYE IN INTERSTITIAL KERATITIS, TREATED AND UNTREATED (Carvill and Derby)

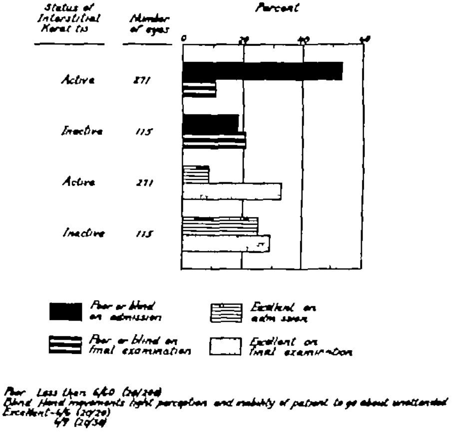
	Patients	End result, visual acuity percentage of patients					
		Excellent 20/20–20/15	Good 20/60–20/40	Practical 20/200–20/70	Fingers	Light perception	Blind
Treated	100	74	12	14	—	—	—
Untreated	93	38	31	18	6	0	2

Their treatment methods are identical with our own. In all their treated patients practical and useful vision was obtained and in 74 per cent the result was full vision in the better eye. This is contrasted with 8.5 per cent of blindness, complete or nearly so and only 38 per cent excellent results in patients untreated. Our own results are fully confirmatory of these.

The results of Klauder and Vandoren, presented in Fig 49, do not lend themselves to strict comparison with those of other observers but are nevertheless in agreement. As one would expect, treatment administered after the acute phase of the interstitial keratitis has subsided and corneal

FIG. 49

COMPARISON OF VISUAL ACUITY ON ADMISSION WITH FINAL VISUAL ACUITY OF PATIENTS WITH ACTIVE AND PATIENTS WITH INACTIVE INTERSTITIAL KERATITIS.
(From Klauder and Vandoren)



scarring has occurred is of limited value in improving vision. However in active cases these treatment results are surprisingly good in the 55 per cent of patients who had poor or no vision prior to treatment, only 11 per cent remained in the category after treatment excellent vision was increased from 10 per cent prior to treatment to 35 per cent at the termination of treatment.

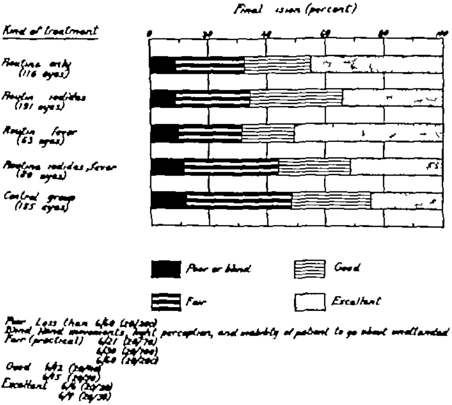
The end results of various treatment plans are shown in Fig. 50 also from Klauder and Vandoren. In this study the best results followed

routine treatment alone or supplemented by fever (malaria, bacterial proteins, etc.) The actual effects of fever therapy are not evident from these figures since the visual acuity of the majority of patients to whom fever was given was on the average much less than in those who were

FIG. 50

FINAL VISUAL ACUITY OF PATIENTS WITH INTERSTITIAL KERATITIS FOLLOWING DIFFERENT PLANS OF TREATMENT COMPARED WITH VISUAL ACUITY OF CONTROL GROUP

(From Klauder and Vandoren)



given routine treatment. A striking finding is the apparent deleterious effect of iodides upon the outcome of acute interstitial keratitis. When employed in conjunction with routine treatment, satisfactory results decreased from 44 to 34 per cent and when administered in conjunction with routine treatment and fever therapy a satisfactory outcome decreased from 54 to 31 per cent. These results clearly contra-indicate the use of iodides in any form in the treatment of interstitial keratitis.

Treatment is successful also in minimizing the incidence of subsequent relapse, so frequent and so dreaded in untreated patients. This too is

shown by Carvill and Derby's figures in Table 74. Relapse occurred in only 3 6 per cent of the treated group as compared with a 27 per cent in-

TABLE 74

INCIDENCE OF RELAPSE IN INTERSTITIAL KERATITIS, TREATED AND UNTREATED (Carvill and Derby)

	Patients	Percentage incidence of relapse
Treated	100	3 6
Untreated	100	27 0

cidence in those untreated. In our own material subsequent relapse occurred in 14 or 10 per cent, of 144 patients treated. It is at least in part related to the inadequacy of treatment, since 5 of our patients had been treated for less than 3 months and 5 for periods ranging from 6 months to 1 year It may occur however in patients receiving thoroughly adequate and intensive treatment. Four patients in our material had been treated for 2, 3 3 and 5 years, respectively before relapse occurred.

The question of prevention of involvement of the uninvolved eye in patients with unilateral interstitial keratitis is of great importance. In Carvill and Derby's series there were 18 patients in Robinson's 44 patients in whom treatment was started while the process involved a single eye. In only 2 of these 62 patients (Table 75) was the normal eye

TABLE 75

INVOLVEMENT OF SECOND EYE IN PATIENTS WITH INTERSTITIAL KERATITIS AS INFLUENCED BY TREATMENT

Author	Number of patients treated for unilateral interstitial keratitis	Subsequent involvement of second eye
Robinson	44	1
Carvill Carvill and Derby	18	1
Lazarescu	101	14
C.C.G	55	16
Klauder and Vandoren	151	60
Totals	369	92

subsequently involved though in the absence of treatment bilateral involvement would have been practically inevitable. The interval over which these patients have been followed ranges as high as 12 years. The experiences of Lazarescu the C C G and Klauder and Vandoren have not been so satisfactory Of 101 cases reported by the former involvement of the second eye occurred in spite of treatment in 14 Among the patients

of the C.C G the process became bilateral under treatment in 16 of 55 patients, and in 60 of 151 of Klauder and Vandoren's patients treatment failed to protect the uninvolved eye. The reason for these differences is not evident. Zimmermann believes that the favorable results in Robinson's patients are due to the fact that the majority of the patients were young adults. In his own large material he has records of only 6 cases of interstitial keratitis in children under 14 which have continued monocular under treatment. He believes that interstitial keratitis in older individuals runs a different and perhaps milder course than in children. The observations of the C.C.G apparently confirm this assumption. Among their cases, involvement of the second eye following treatment was not noted in patients over 5 years of age In contrast, treatment failed to prevent spread to the uninvolved eye in 38 per cent of patients under 5 years of age. Although no data are available as to age, Klauder and Vandoren found that the frequency with which interstitial keratitis remained monocular is appreciably influenced by the duration of the eye involvement at the time treatment is started. In only 33 per cent of patients in whom treatment was begun within the first month was the uninvolved eye protected. In contrast, the process remained monocular in 51 per cent of patients in whom treatment was not instituted until after the first month. Although this suggests that early treatment of interstitial keratitis may hasten the involvement of the second eye, it seems much more likely that in addition to treatment, the patient's defense mechanism plays an important part in determining the course of the disease process and that in some instances involvement of the second eye may be inevitable.

It is difficult to reconcile the favorable results of American investigation with the pessimism of workers abroad. Hersau and Hossmann for example reporting on a large series of patients, think that the results are no better now with modern intensive treatment than in the pre-arsphenamine era. We cannot understand their poor results but we can testify unequivocally and from personal observation as to the correctness of the conclusions described above.

An outline of treatment suggested by Klauder and Vandoren —The following scheme of treatment of interstitial keratitis is recommended in the excellent paper of Klauder and Vandoren

Fever Therapy

Malaria or hyperthermy should be employed as soon after onset as possible If these types are not available another fever-producing agent should be substituted. Because arsenicals and bismuth are anti-malarial, they should be withheld during the course of induced malaria, but should be given in the intervals between fever bouts produced by other agents.

Antisyphilitic Treatment

Neoarsphenamine or another trivalent arsenical (in full doses* in propor

* Although initial use of large doses of an arsenical is generally to be avoided in treatment of other acute ocular lesions of syphilis because of the danger of Herxheimer's reaction in the involved eye, pragmatically this does not apply to interstitial keratitis. It is apparent that this procedure in treating interstitial keratitis very rarely aggravates the disease in the eye or in other organs.

tion to body weight) and bismuth subsalicylate should be given in alternating courses Soluble bismuth, however should be employed at the onset of treatment, simultaneously with arsenical therapy The treatment should be continued according to the following schedule until approximately 30 injections of the arsenical and 60 of the bismuth have been administered.

Weeks 1– 9 Neoarsphenamine, 10 weekly doses
Bismuth (soluble) 8 doses twice weekly during first month
10–19 Bismuth, 10 weekly doses
20–29 Neoarsphenamine, 10 weekly doses
30–39 Bismuth, 10 weekly doses
40–44 Neoarsphenamine, 5 weekly doses
45–54 Bismuth, 10 weekly doses
55–59 Neoarsphenamine 5 weekly doses
60–69 Bismuth, 10 weekly doses
70–73 Rest period
74–83 Bismuth, 10 weekly doses

Riboflavine in the treatment of interstitial keratitis—Although no large series of cases has been reported the observations of Kruse and of Sydenstricker who successfully treated 2 and 5 cases respectively of interstitial keratitis with riboflavine are potentially of great importance. Our experience in 6 patients is much less satisfactory Nevertheless should this type of therapy prove uniformly successful in the management of this complication of congenital syphilis it must be remembered that it is only an adjunct to the systemic treatment of the disease.

The non-specific treatment of interstitial keratitis—Various workers impressed with the relative inefficacy of antisyphilitic treatment (perhaps because of their failure to make it intensive enough) have tried such various non-specific measures as malaria, the intramuscular injection of milk or the intravenous injection of typhoid vaccine. Although Meller and Schreiber have found such measures of no particular benefit, we agree with Klauder and Vandoren that they are of distinct value in cases resistant to intensive routine therapy

The roentgen ray treatment of interstitial keratitis—This is a method which we have used in only two cases, unfortunately with poor results in both. It has been highly praised by various German investigators particularly Löwenstein as of value especially in patients with corneal opacities resistant to ordinary therapeutic measures. Löwenstein treated 9 patients with severe interstitial keratitis of more than 6 months duration. In all, the cornea before treatment was dense gray or white. In all vision in the better eye was restored to 6/8–6/6 practically without residual scarring. His technique is as follows

The patient's face and hair are covered by a lead mask in which there is a circular window 4 cm. in diameter for the eye. About 1.5–2.0 Holzknecht units are given from a focal skin distance of 30 cm through 4 mm. of aluminum filter employing 120 K.V and 4 M.A Using these factors

15 per cent skin erythema dose equals 80–90 r A total of four or five treatments is given at weekly intervals.

Löwenstein did not administer simultaneous antisyphilitic treatment though other workers have combined roentgen-ray and drug therapy with equally satisfactory results. Antisyphilitic treatment should of course be employed, as much for the sake of the patient s general health as for the ocular lesion. Roentgen-ray therapy may be reserved as an adjunct measure for those patients failing to improve rapidly on intensive treatment, or in whom there seems likely to be permanent residual corneal scarring

Ocular Operations in Patients with Syphilis

The well-known influence of trauma in the etiology of syphilitic lesions is a point of importance with reference to the question of operation on the eye of a patient with syphilis. Puscariu has reported plastic iritis developing in the eyes of 15 patients following cataract extraction and that 9 of these patients had syphilis. In the Wilmer Ophthalmological Institute this sequel of operation has been observed only once. However ophthalmologists frequently hesitate to adopt operative procedures on the eye of a syphilitic patient, whether or not ocular lesions of syphilis are present, for fear of inciting the appearance of new lesions or the exacerbation of old ones

In our experience two types of ocular operations have most frequently brought this question to the fore. These are for glaucoma arising from an old syphilitic uveitis and for cataract extraction in elderly individuals in whom the existence of syphilis is discovered during pre-operative study by means of routine positive serologic tests. In general, the ophthalmologist's attitude toward surgical interference in the eye of a patient with syphilis should be that of the general surgeon toward operations elsewhere in the body namely that the existence of syphilis and in particular the presence of positive serologic tests, is not a contra-indication to operation. If the situation demands an emergency operation, it may be performed at once to be followed immediately by antisyphilitic treatment. If the operation is one of election it is advisable to precede it by a course of 4 to 8 weeks treatment which may be resumed to whatever extent necessary after operation. It is never necessary or desirable to "wait until the serologic tests are negative. This result may never be achieved and the patient may thus be deprived of a vision-saving procedure.

To meet the specific situations of operations for glaucoma or cataract, it is well to recall that the former condition usually arises in relatively youthful patients as a direct result of a syphilitic ocular lesion and that treatment should be carried through before and after operation with the intensity and to the extent necessitated by the patient's age probable life expectancy potential infectiousness, and the type of syphilitic involvement of other organs than the eye. In other words a complete course of treatment lasting 18–24 months or longer is usually desirable. Patients with cataract, however are usually elderly individuals with a syphilitic infection which is either completely latent or has done the patient com

paratively little harm. Here the desideratum of antisyphilitic treatment is merely the prevention of a possible syphilitic lesion in the eye after operation. Treatment should be mild and of such a character as not to disturb the patient during the period of 10 days or so of post-operative absolute quiet demanded by the operation. Mixed treatment by mouth for a week immediately after operation followed by 3-6 small doses of neoarsphenamine (0.3-0 45 gm.) is all that is ordinarily necessary or desirable This may even be accomplished without telling the patient of the diagnosis of syphilis if it is desired to spare him this added shock.

The situation in patients with congenital syphilis is apparently different from that in patients in whom the infection is acquired. Klauder in a study of the precipitating factors of interstitial keratitis, found that it frequently appeared following trauma, and in one series of cases he reviewed (Butler's) operation on or around the eye appeared to be responsible in several instances. However as pointed out by Klauder, it is extremely difficult to determine the exact rôle of trauma in precipitating interstitial keratitis unless it appears immediately after injury Nevertheless it has been reported so frequently that, unless faced with an emergency operations upon or around the eyes of individuals with congenital syphilis should not be attempted until the patient has been adequately treated

The Non-Specific Effects of Antisyphilitic Treatment on Ocular Lesions Due to Other Causes Than Syphilis

Stokes, O Leary and Moore have each called attention to a phenomenon familiar to ophthalmologists namely that antisyphilitic treatment, and the arsphenamines in particular sometimes exercise a marked nonspecific effect on non-syphilitic inflammatory lesions in the eye (particularly brucellosis?) We have seen 14 patients with chronic uveitis in whom the most exhaustive search had failed to reveal any evidence of syphilis in whom other methods of treatment, including tuberculin non-specific protein and extirpation of all conceivable foci of infection had failed to bring about any amelioration of the ocular lesion and in whom prolonged arsphenamine treatment, given as a last resort produced definite improvement. In 8 of these, there was secured a complete and permanent cure.

So far as ocular syphilis is concerned this non-specific effect of treatment requires to be carefully considered when an arsphenamine (or to a lesser extent, the heavy metals) is given as a therapeutic test for a suspected but not definitely proved syphilitic lesion of the eye. A false positive favorable result may lead the unwary physician into an erroneous diagnosis of syphilis with its far reaching personal and social implications

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Chapter XXI

ASYMPTOMATIC NEUROSYPHILIS

The studies carried out in our own clinics and elsewhere throughout the world have thrown much light on important questions relating to the development of syphilis of the central nervous system. It is impossible intelligently to treat syphilis in any stage of the infection without a thorough working knowledge of these essential facts. The discussion of this chapter is largely drawn from our own publications, the conclusions of which are confirmed by many investigators beginning with Ravaut's pioneer efforts of thirty years ago and continuing until the present.

Invasion versus involvement of the nervous system — Invasion of the nervous system by the treponeme probably occurs in all patients with syphilis and, unless the course of the disease is influenced from without (by treatment) this takes place in most, if not in all instances within the first year after infection. This statement is based on the high incidence of spinal fluid abnormalities in patients with untreated early syphilis (50–75 per cent reported by some observers) and on the fact that in a few instances treponemes may actually be present in a spinal fluid which is otherwise normal. In spite of this apparent constancy of neuraxis invasion, however relatively few patients later develop actual tissue involvement manifested by obvious clinical signs of neurosyphilis. The proportion developing such lesions is markedly influenced by at least two definite factors race and sex (Table 76) All forms of late neurosyphi-

Table 76
The Incidence of Neurosyphilis in Patients with Late Syphilis, by Race and Sex, based on 6420 Patients with Late Syphilis
(Turner)

Type of Neurosyphilis	Percentage of all patients with late syphilis developing specified type of neurosyphilis, by race and sex			
	White		Negro	
	Male	Female	Male	Female
General paresis and taboparesis	8.4	5.0	2.0	0.3
Tabes dorsalis	13.9	4.6	3.5	0.8
Vascular	1.3	0.3	2.4	0.6
Diffuse meningovascular	15.4	12.2	13.7	5.5
Total	39.0	22.1	21.6	7.2

lis are more frequent in males than in females and (excepting purely vascular involvement) in white patients than in Negroes. The incidence of nearly 40 per cent in white males is in striking contrast to that of only 7 per cent in Negro females.

If it is true that invasion of the nervous system occurs in all patients recently infected with syphilis, why does not clinical neurosyphilis develop even more frequently? If we eliminate from consideration the unknown factors affording protection to females of either race or to Negroes of either sex, and for the moment limit ourselves to a consideration of white males with previously untreated late syphilis, it can be shown that four groups are readily separable

1. Those having already developed clinical evidence of neurosyphilis—about 40 per cent.

2. Those with abnormal spinal fluids but as yet no clinical evidence of damage—about 18 per cent. This group is potentially liable to the subsequent development of definite neuraxis lesions

3 Those with normal spinal fluids but with minor neurologic abnormalities (unequal, irregular or sluggishly reacting pupils or unequal, exaggerated or diminished reflexes) not in themselves diagnostic of neurosyphilis, but constituting suggestive evidence of early neurologic damage. It is probable that these are instances of neurolatency the so-called "burnt out" neurosyphilis in which spinal fluid abnormalities once present have disappeared, though minor neurologic changes remain as a scar of the formerly active inflammatory process in the nervous system. About 33 per cent of all patients with late syphilis fall in this group

4. Those who show neither clinical nor serologic evidence of nervous system involvement.

The first three of these categories include about 90 per cent of all white males with untreated late syphilis. The remaining 10 per cent may be explained either on the ground of faulty observation, or that the nervous system has escaped invasion, or that sufficient local tissue immunity has been available before or after invasion to protect the patient against the development of either clinical or serologic abnormalities.

The detection of asymptomatic involvement of the nervous system by routine spinal fluid examination.—If invasion of the nervous tissues is sufficiently extensive or if the protective mechanism in this group of structures is so lacking as to permit actual tissue involvement to occur the involvement may be detected almost as soon as it has developed or at any time thereafter by means of routine examination of the spinal fluid. If spinal fluid abnormalities are present in the absence of clinical evidence of neurosyphilis the condition is known as asymptomatic neurosyphilis. The importance of routine lumbar puncture and the absolute necessity of carrying it out in every patient with syphilis, early or late is apparent from the fact that spinal fluid abnormalities antedate the appearance of obvious clinical damage in the nervous system by many years. The potential paretic or tabetic patient is recognizable within the first year of the infection, rather than 15 years later when irreparable harm may already have been done. As the latent syphilitic can only be

recognized by means of routine serologic tests so can the latent neurosyphilitic only be discovered by means of routine spinal fluid studies. If this condition is recognized before the development of clinical symptoms and signs, these may usually in fact almost always be prevented by appropriate modifications of treatment. The physician who omits to perform a routine spinal puncture in every patient diagnosed as syphilitic is indeed negligent. Just when spinal puncture should be done, how often to anticipate spinal fluid abnormalities the factors in the patient or in treatment which influence their incidence, their interpretation when present, their influence on the ultimate outcome in the individual patient, form the subject matter of the following paragraphs.

The classification of asymptomatic neurosyphilis.—The type of spinal fluid change discovered is at least to some degree indicative of the extent and type of neurologic damage and of the ultimate prognosis. For convenience in study and discussion patients with early or late asympto-

TABLE 77

TYPICAL SPINAL FLUID ABNORMALITIES IN INDIVIDUAL PATIENTS WITH EARLY OR LATE ASYMPTOMATIC NEUROSYPHILIS

Group	Cells	Globulin	Wassermann	Colloidal Curve
I	12	0	0 with 1 0 cc.	0000000000
	8	+	0 with 1 0 cc.	2110000000
II	6	++	0 with 1 0 cc.	3210000000
	2	++	0 with 1 0 cc.	4432100000
	30	+	4 with 1 0 cc.	1110000000
	0	+++	4 with 0 6 cc.	5542100000
	42	+	4 with 0 1 cc.	1110000000
III	87	++++	4 with 0 1 cc	5555432000
	120	++	4 with 0 2 cc.	5542100000

matic neurosyphilis may be divided into three groups on the basis of the character of the changes in the spinal fluid. Group I includes patients with minimal serologic abnormalities (increased cell count and/or globulin content with other tests negative) Group III those with maximal changes (the paretic formula) and Group II those with fluids of an intermediate type.*

The frequency of asymptomatic neurosyphilis.—The incidence of these fluid abnormalities in various stages of syphilitic infection varies with the time after infection at which spinal puncture is done and with the amount and character of previous treatment. Leaving this latter factor out of consideration the proportion of the various types of fluid changes in seronegative and seropositive primary early secondary and various types of late syphilis (excluding from all groups those patients

* An acute syphilitic meningitis is sometimes recognizable by routine spinal puncture in early syphilis just before the development of signs and symptoms, by virtue of a high cell count in the cerebrospinal fluid, 150 or more cells Other abnormalities may be either present or absent.

with definite clinical evidences of neurosyphilis) is shown in Fig. 51 There is a steady rise in the early stages of infection, and a sharp drop between early secondary and late syphilis. This drop is due to the fact that almost exactly this proportion of patients (18–20 per cent) have developed, with the passage of years frank evidence of clinical neurosyphilis. As between various types of late syphilis (cutaneous, osseous cardiovascular visceral, latent, etc) there is very little evidence of protection of the nervous system the incidence of asymptomatic neurosyphilis is about the same in all.

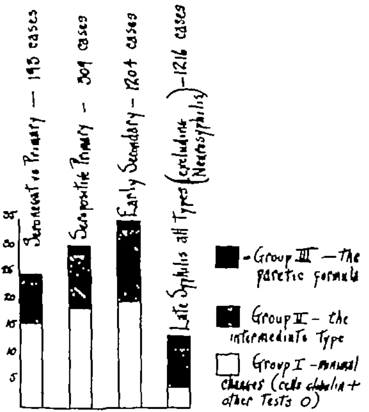


FIG. 51 —The incidence of asymptomatic neurosyphilis in various stages of syphilitic infection. (Early syphilis based on data of C.C.G late syphilis on data of Moore and Faupel.)

The influence of treatment in the development of asymptomatic neurosyphilis —The effect of the amount of treatment administered prior to routine spinal puncture on the incidence of abnormalities of the spinal fluid is shown in Fig 52. Here one observes several interesting phenomena. The abnormalities of Group I fluids tend to disappear rapidly after treatment, this being more apparent in early than in late syphilis In early and late syphilis both Group II fluids tend to increase after one or two courses of treatment this accounting for the aggregate

increase. Only after three or more courses of treatment is there a marked fall in Group II fluids in either class of patients. This preliminary rise is difficult to explain, it may, at least in early syphilis be due partly to the effect of lapsing or intermittent as compared with continuous treatment. Another probable factor is that the type of abnormal fluid may depend on the exact time of puncture. In other words, a patient whose fluid studied today is found to be Group I in type, might show a Group II or III fluid if puncture had been delayed a month or two The ineffectiveness of routine treatment in reducing the incidence of Group III fluids especially in early syphilis, is clearly shown.

The character of treatment is of great importance in influencing the probability of spinal fluid abnormalities in early but not in late syphilis In early syphilis, asymptomatic neurosyphilis is almost three times as frequent when treatment is irregular as when it is carried out without rest periods of any kind, and Group III fluids are increased tenfold by allowing

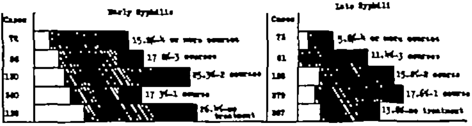


FIG. 52 —Incidence of abnormal spinal fluids in patients with early syphilis and those with late syphilis, after varying amounts of treatment. (Moore and Faupel.)
In this and in similar succeeding figures the white blocks represent Group I (minimal change) the cross-hatched blocks Group II (intermediate type) the solid black blocks Group III (paretic formula) fluids.

treatment to lapse In late syphilis on the contrary no such effect is apparent (Fig 53) Here one finds only a slight increase in the incidence of abnormalities of the spinal fluid after intermittent treatment, and even this is probably accounted for by the inclusion of a number of relatively early cases in the group of latent syphilis. The difference in this respect between early and late syphilis is we believe wholly accounted for by the fact that in early syphilis immunity is in the process of establishment and may be suddenly altered or temporarily abolished by antisyphilitic drugs. Undestroyed foci of organisms in the nervous system to which penetration of the arsphenamines is notoriously difficult, may then multiply without any hindrance from the patient's own defence mechanism. In late syphilis on the other hand immunity is so firmly established (and probably extended to include the tissues of the nervous system) that the spinal fluid undergoes slight if any alteration from the shock of treatment. From this standpoint, then one may conclude that in late syphilis continuous treatment is by no means so essential as in early syphilis and a rest period probably does no harm

When to perform routine spinal puncture —The optimum time

for performing spinal puncture is a matter of considerable importance to the practicing physician. In early syphilis, and provided that treatment is carried out with absolute regularity, it is our present practice to test the fluid after the second course of arsphenamine (at about the sixth month of treatment) Fig. 54 shows, however, that disregarding the character of treatment, the highest incidence of abnormalities of the spinal fluid in early syphilis is at about the eighteenth month after infection. If one is dealing with a patient who cooperates, puncture may safely be performed at about the sixth month and if the fluid is negative, need not be repeated until the end of the patient's year of probation. If the patient allows frequent lapses to interfere with the regularity of his treatment, puncture should be performed early and should be repeated between the eighteenth and twenty-fourth months of the infection particularly if there has been a clinical or serologic recurrence in the interim. It is rarely worth while to perform puncture on a patient with early syphilis before any treatment is given because a negative result may be obtained in a fluid which if tested later might be positive. In this connection Chesney and Kemp have found that the spinal fluids of many patients with early syphilis negative to routine test are infectious for rabbits (the spinal fluid abnormalities, being an expression of inflammatory lesions in the tissues do not appear over night but require weeks for their production)

In late syphilis whether or not the patient presents any neurologic abnormalities, lumbar puncture should be carried out as soon as possible after the diagnosis is made. If this is not done, a good deal of valuable time may be wasted and unnecessary expense accrue to the patient by virtue of the prolonged administration of treatment inadequate to control the infection in the nervous system. If it is done, treatment may be promptly adapted to the needs of the situation. The only exceptions to routine spinal fluid study in late syphilis are (a) in patients with suspected brain tumor (b) during preg

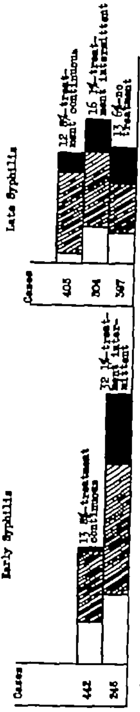


Fig. 54.—Incidence of abnormal spinal fluids in patients with early syphilis and in patients with late syphilis, whose treatment was continuous as contrasted with those in whom it was intermittent. (Moore and Faupel.)

nancy (c) in elderly patients i.e. those over 60 presenting no clinical evidence of neurologic damage and (d) in those patients whose illness from other standpoints is so serious as to render the question of asymptomatic neurosyphilis unimportant, as in cardiovascular syphilis.

The relationship of seroresistance to asymptomatic neurosyphilis.—In patients with early syphilis the persistence of a positive serologic test of the blood after 6 months or longer of treatment is strongly suggestive evidence that the spinal fluid is also abnormal. This is clearly

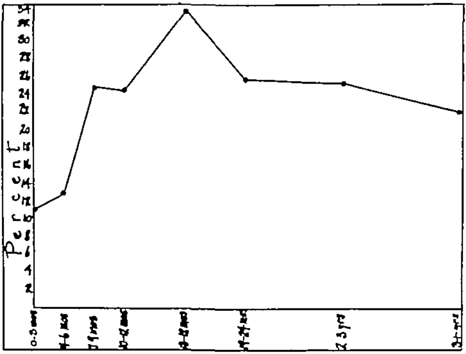


FIG 54.—Incidence of abnormal spinal fluids in syphilis from the standpoint of the duration of the infection before spinal puncture. (Moore and Faupel.)

shown in Fig. 55 Not only is this true, but the more abnormalities present in the fluid the greater the probability that the patient will be seroresistant during early treatment. As we have elsewhere pointed out this association is next to the influence of intermittent or irregular treatment the commonest cause of a persistently positive serologic test in early syphilis. The most frequent question asked by the practitioner is what to do for a patient whose serologic tests refuse to reverse under treatment The immediate counter of the expert is another question—what does the spinal fluid show? (See also Chapter XXVIII)

In late syphilis however asymptomatic neurosyphilis is not a particularly common cause for seroresistance. Differences in the incidence of abnormal spinal fluids when the blood test becomes negative or remains positive after a given amount of treatment are hardly apparent until at least three or more courses have been administered. At this stage of the

infection a persistently positive test is much more likely to be due to bone visceral, or cardiovascular involvement than early in the disease.

Although persistently positive serologic tests in early syphilis are frequently indicative of asymptomatic neurosyphilis negative tests do not mean freedom from neuraxis involvement. In a study of 297 cases of asymptomatic neurosyphilis unfortunately not classified as to early or late, Menninger and Bromberg found that regardless of the factor of

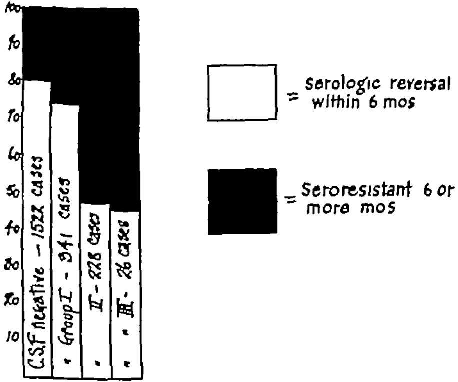


FIG. 55.—The relationship of seroresistance and of asymptomatic neurosyphilis in patients with early syphilis (Data of C.C.G.)

treatment, 33 per cent had negative blood (Kahn and Wassermann) tests. Of 83 untreated patients, 19.0 per cent had negative blood but positive spinal fluid tests. This is in agreement with our experience. While the discrepancy between the results of the examination of the blood and spinal fluid might become less as more sensitive serologic tests are employed there is at present no means of detecting asymptomatic neurosyphilis except by routine examination of the spinal fluid of all patients with syphilis.

The prognosis of asymptomatic neurosyphilis —The force of the syphilologist s insistence on the routine performance of spinal fluid examination in all patients with syphilis would be lost if he were not able to supply a direct answer to the following pertinent questions What is the

significance of spinal fluid abnormalities in patients who are clinically normal? Do they tend spontaneously to disappear? What is their relationship to the ultimate prognosis? Definite information on these points has been provided by studies from the Johns Hopkins clinic, and by the C C G

So far as early syphilis is concerned the influence of spinal fluid abnormalities on the probability of an ultimately satisfactory outcome i.e. persistent clinical normality and serologic negativity is clearly shown in Table 78 based on the data of the C C G Sixty-four per cent of patients

TABLE 78

THE EFFECT OF CEREBROSPINAL FLUID ABNORMALITIES (ASYMPTOMATIC NEUROSYPHILIS) ON THE ULTIMATE OUTCOME IN EARLY SYPHILIS
(Data of C.C.G)

Cerebrospinal fluid results	Total cases	Percentage with satisfactory outcome
C.S.F not tested	271	44 6
Negative	725	64 7
Group Ia—Cell count 6 or over all other findings negative	89	57 3
Group Ib—Cell count 5 or over excess protein, Wassermann and colloidal test negative	98	36 7
Group II—Cells and protein + or − Wassermann partial positive, colloidal test + or −	145	27 6
Group III—Paretic formula	32	0 0

whose fluids were known to be normal achieved a satisfactory result. With increasing degrees of spinal fluid abnormality the percentage of favorable outcomes diminishes rapidly to zero in those patients with maximal fluid changes (Group III)

This is perhaps even better shown by our own more limited but nevertheless thoroughly studied material. Hopkins and Moore have followed with periodic re-examinations over an average period of 8 years a fairly large series of patients with early and late asymptomatic neurosyphilis and for comparison a much larger series of patients with early and late syphilis who were neurologically normal on admission and whose spinal fluids were negative The results, startling even in this relatively short period of observation are presented in Fig. 56. Of the patients with normal fluids only 3 6 per cent developed definite or questionable evidence of neurosyphilis (in all instances meningeal or meningovascular in type) Of the patients with group II asymptomatic neurosyphilis the analogous figures are 32 per cent of those with group III (paretic formula)

fluids, 78 per cent, and in this latter group 30 per cent of the total number of patients have already developed parenchymatous neurosyphilis (tabes dorsalis or general paresis)! Unfortunately our information as to the ultimate neurologic fate of individuals with minimal fluid changes (group I) is too incomplete for presentation on a statistical basis but even in this group we have observed the subsequent development of clinical evidence of neurosyphilis in more than a dozen patients.

The prognosis of asymptomatic neurosyphilis is equally gloomy whether discovered early or late in the course of infection, *unless the development of clinical neurosyphilis is prevented by appropriate intensification or modification of treatment.* Spontaneous regression of Group II and III spinal fluids to normal is in our experience a rare phenomenon. Not only is the

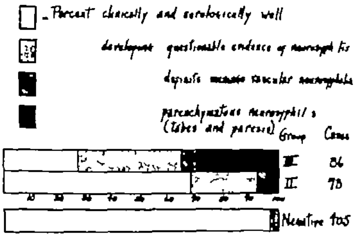


FIG. 56.—The prognosis of early and late asymptomatic neurosyphilis compared with that of patients with normal spinal fluids in early and late syphilis. (Data of Hopkins, and of Moore and Hopkins.)

physician justified in warning such a patient of the likelihood of the development of serious neurologic damage, but he may even predict with some accuracy that if the fluid shows the paretic formula (group III) even so soon as within the first year of infection, there is a strong probability that the type of the expected neurosyphilis will be tabetic or paretic.

The prognostic significance of a normal spinal fluid.—The prognostic import of a normal spinal fluid has been thoroughly investigated by Lomholt. The situation differs depending on the stage of infection the time at which the fluid examination is carried out, the character and amount of previous or subsequent treatment, and the occurrence of clinical or serologic relapse. Supposing that the fluid of a patient with early syphilis has been found to be normal after 6 months of treatment, it will be found to be normal (with very few exceptions) at any later date, provided that a lapse in subsequent treatment does not permit a second period of generalization of the treponemes (spirochetemia). Such a second generalization is usually manifest by a clinical or a serologic relapse or

both and if it occurs repetition of spinal fluid study should be carried out just as if the patient had been freshly infected i.e. after 6 months of treatment. In a patient with early syphilis whose spinal fluid once negative is subsequently found to be positive unless the initial examination was made very shortly after infection, careful search will almost invariably reveal that a clinical or serologic relapse has occurred since the *original fluid examination. If after the original negative cerebrospinal* fluid there is no evidence of clinical relapse and if the serologic tests remain persistently negative, lumbar puncture need not be repeated until the end of the post-treatment year of probation. If again negative at this examination the test need never be repeated in the average patient.

In patients with late syphilis (of more than 4 years duration) the establishment of immunity is so firm that redissemination of virus probably does not occur even under the disturbing effect of inadequate treatment. If the cerebrospinal fluid is found to be normal in such individuals (who are of course free from obvious neurologic damage) * lumbar puncture need never be repeated Unless under exceptional circumstances such as invasion of the nervous system by direct extension from a neighboring focus of syphilitic inflammation (as in periostitis of the inner cranial table) subsequent fluid examinations will always be normal.

Not only does a negative examination of the cerebrospinal fluid either in early or late syphilis, afford a practical guarantee against the subsequent development of fluid abnormalities (except in the circumstances enumerated) but also it affords equally satisfactory security against the later appearance of grave signs or symptoms of neurologic damage. Among a large series of patients with early syphilis and negative fluids this eventuality occurred in only 5 per cent, and in all of them the clinical neurosyphilis was mild of the meningeal neurorecurrent type, and easily amenable to treatment. In a larger similar series of patients with late syphilis, the incidence of development of subsequent clinical neurosyphilis was only 0.8 per cent (Moore and Hopkins) We have never observed the appearance of tabes or paresis in a patient with a previously known negative spinal fluid (unless there has been interim evidence of regeneralization of treponemes) The only serious mental reservation which the physician needs to make in congratulating his patient on his almost certain freedom from subsequent neurosyphilis is in connection with the possibility of a more or less purely vascular involvement, endarteritis of a vessel deeply seated in nervous tissue.

The treatment of asymptomatic neurosyphilis —This subject is more fully discussed in Chapter XXIV Here it is desirable only to point out that routine antisyphilitic treatment, of a character and intensity adequate to deal successfully with patients with no clinical or serologic

* It is of course known to every physician of experience that in some patients with outspoken clinical evidence of neurosyphilis, particularly of the tabetic and vascular varieties, the cerebrospinal fluid may be completely normal, even though the neuraxis lesion is still progressive. Such cases are not intended to be included in the discussion of this chapter which refers only to patients who show no detectable neurologic changes.

evidence of neuraxis involvement is usually inadequate for those in whom asymptomatic neurosyphilis is discovered. Intensification of routine treatment the use of subdural medication of tryparsamide of fever therapy or of all four of these measures, may be necessary to accomplish the desired result of maintained clinical normality and serologic negativity In most instances treatment must be prolonged far past the point necessary in more fortunate patients with normal fluids.

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CHAPTER XXII

THE INCIDENCE, PROPHYLAXIS, AND PROGNOSIS OF NEUROSYPHILIS

TO AN even greater extent than elsewhere in this book the discussion of methods and results of treatment in neurosyphilis is a record of the personal experience of the workers of the Johns Hopkins clinic The bibliography of the subject is so vast that a critical review of it would fill a volume of its own certain points are still so unsettled or so controversial that a detailed consideration of them would serve but to confuse the practitioner Within the limits of this monograph, it is possible to discuss only relatively broad general principles. These principles unfortunately are not so readily applicable to the individual patient as is the case with the simpler problems of early and benign late syphilis. Each neurosyphilitic patient is a problem unto himself to be solved if at all, only after full consideration of many factors. Individualization of therapeutic approach is essential. It is not possible accurately to answer the question 'how shall one treat neurosyphilis. To be answered satisfactorily the question must be rephrased to 'how shall one treat this particular neurosyphilitic patient? Success in therapy in this type of syphilis implies some things which no text can supply namely a basic knowledge of neurology psychiatry and internal medicine a working acquaintanceship with the art as well as with the science of medicine, and experience. Lacking any one of these, the practitioner will secure better results with his patients if he carries out treatment procedures which have been advised for the particular individual patient by a consultant expert.

The classification of neurosyphilis —As elsewhere in the body syphilis in the nervous system may produce such a wide variety of lesions that almost any neurologic disease may be aptly mimicked. It is possible to subdivide neurosyphilis into many more or less clearly recognizable disease entities, some of which are common, some rare. More simply from the standpoint of the therapist, a classification may be made on the combined clinical and anatomic basis proposed by Head and Fearnsides and further modified by others. This divides patients into four groups depending on the extent to which the pathologic lesion is predominantly meningeal, vascular or parenchymatous the clinical picture predominantly on an inflammatory or a degenerative basis as follows

1 More or less purely meningeal neurosyphilis. This is almost always an early manifestation occurring within the first two years of the infection. It includes acute syphilitic meningitis most neurorecurrences and early asymptomatic neurosyphilis.

2 More or less purely vascular neurosyphilis. This may occur early or late usually the latter It depends on the existence of a localized or widespread syphilitic cerebral endarteritis sometimes with but often without

associated meningeal or parenchymatous involvement. It is frequently found in association with cardiovascular syphilis apparently as part of a widespread involvement of the blood vessels. It causes cerebral vascular accidents hemiplegias monoplegias paraplegias, subarachnoid hemorrhage, etc.

3. Diffuse meningovascular neurosyphilis, in which the lesions are a mixture of meningeal and vascular involvement. Parenchymatous changes may or may not be present if they occur they are usually minimal and rarely enter into the clinical picture. This group includes such widely diverse clinical entities as brain gumma, syphilitic epilepsy diffuse 'cerebrospinal syphilis and late asymptomatic neurosyphilis.

4. More or less purely parenchymatous neurosyphilis including tabes, paresis, and primary optic atrophy (whether or not associated with tabes)

In the first three of these groups, the inflammatory element predominates in the last, the degenerative element. This is the obvious *a priori* explanation for the fact that treatment efforts are more successful in the first three than in the last group and in any individual case successful in proportion to the extent to which inflammatory changes predominate over degenerative lesions.

The frequency of neurosyphilis —Grouping together all patients infected with syphilis, disregarding the factors of race and sex, and whether untreated or treated by the older methods preceding the introduction of the arsphenamines, about 25 per cent will ultimately develop clinical evidence of involvement of the nervous system. The incidence of neurosyphilis in patients treated by more modern methods cannot as yet be so accurately determined the interval between infection and the development of neurologic symptoms is long (12–25 years) and the mass employment of modern methods has been in use for too short a time for definite facts to be available on a large scale. The type of neurosyphilis will be paretic in about 5 per cent of those infected, tabetic in about 5 per cent, and diffuse meningovascular in about 15 per cent. Neurosyphilis is an even more serious problem than cardiovascular syphilis it is probably responsible for as many deaths and certainly for much more partial or complete permanent incapacity

The relationship of asymptomatic to symptomatic neurosyphilis —The practitioner will have much less opportunity to exercise his neurologic or psychiatric knowledge if he remembers one simple fact that the appearance of clinical symptoms and signs of neurosyphilis is in most instances preceded by a period of years dating from shortly after the time of infection, during which the existence of neuraxis involvement is readily demonstrable by means of the procedures of routine lumbar puncture and examination of the cerebrospinal fluid. Not only is this true, but it is even possible to predict with some degree of accuracy whether the subsequent clinical involvement to be expected (unless prevented by treatment) will be parenchymatous (tabetic or paretic) or meningovascular in type. And finally as we shall show presently it is possible in many instances, if not in all, to prevent the development of symptomatic neurosyphilis.

A more detailed discussion of asymptomatic neurosyphilis appears in Chapter XXI.

The influence of treatment on the development of neurosyphilis.—The factors influencing the development of neurosyphilis, such as immunity, special strains of organism with a predilection for nerve tissue, bodily constitution, race, sex, alcoholism, mental strain, etc. cannot be elaborated upon in a text devoted to therapy. Though important they are in any case largely beyond the control of the physician. It is essential, however, to enquire into the effect of treatment on the development of various forms of neurosyphilis. So far as asymptomatic neurosyphilis is concerned, this problem has already been discussed in part in Chapter XXI, where we have shown that in early, but not in late, syphilis the incidence of abnormal spinal fluids is more frequent following inadequate irregular treatment, and both in early and late syphilis decreased by prolonged continuous treatment. Unfortunately, even very prolonged and intensive treatment (excluding fever therapy) does not eliminate abnormal fluids which persist in about 5 per cent of all patients infected. In such patients, usually those with maximal fluid changes, the ultimate prognosis is grave, the development of clinical evidence of neurosyphilis common.

The extent to which treatment or the lack of it influences the development of various forms of clinical neurosyphilis is a more difficult problem approachable from two angles. Various observers, including ourselves, have followed over long periods of time patients with early syphilis given varying amounts of treatment. Others have attempted to evaluate the effect of modern treatment methods by a study of the incidence of and death rate from paresis and tabes in the general population. The results of both types of study may be summarised as follows.

The incidence of early meningeal neurosyphilis (acute syphilitic meningitis, early vascular accidents) is increased at least tenfold by the inadequate treatment of early syphilis. Among untreated patients, this form of neurosyphilis is a comparative rarity, occurring in our own material in about 0.3 per cent of cases of early syphilis. Among patients inadequately treated (inadequate treatment for this purpose being defined as less than 12 doses of an arsphenamine with heavy metal) and especially if treatment is carried out at irregular intervals, the probability of development of meningeal neurosyphilis (neurorecurrence) rises to 2–3 per cent. On the other hand, if treatment is continuous for at least 8 months (more than 20 injections of an arsphenamine plus heavy metal) this type of neurosyphilis practically disappears. The inadequate treatment of late syphilis does not predispose the patient to the development of meningeal lesions.

About 10–15 per cent of untreated patients may be expected to develop some clinical manifestation of late neurosyphilis of the type usually classified as diffuse meningovascular. Even relatively inadequate treatment for early syphilis will decrease this probability materially, say from about 15 per cent of those infected to 5–10 per cent. Adequate treatment, as defined in the discussion of early syphilis, will eliminate it almost altogether, or at least reduce it to the low figure of 1–2 per cent.

The expected incidence of paresis (5–6 per cent) and of tabes (3–5 per cent) among untreated patients is not materially influenced in either direction by inadequate treatment and even prolonged intensive adequate treatment of early syphilis with the arsphenamines and heavy metals will not eliminate the possibility of these two disasters entirely About 1–3 per cent of patients, no matter how well treated by routine methods, will fall victims to these forms of parenchymatous neurosyphilis. The hope of their elimination lies in their preclinical recognition by means of routine lumbar puncture and on the addition to routine treatment of tryparsamide and fever therapy

Thus treatment, adequate or inadequate appears to have no influence in increasing the incidence of any form of clinical neurosyphilis except acute syphilitic meningitis Instead, adequate treatment effects a marked reduction in the incidence of late diffuse meningovascular neurosyphilis and a moderate reduction in that of paresis and tabes. If, however treatment does not predispose to the development of clinical neurosyphilis, it does especially if inadequate, definitely shorten the interval between infection and the appearance of symptoms of neurosyphilis. This is clearly indicated by the studies of Hopkins and of Kemp, shown in Tables 79 and 80

TABLE 79

EFFECT OF TREATMENT ON THE INCUBATION PERIOD OF NEUROSYPHILIS FROM THE TIME OF INFECTION TO THE APPEARANCE OF SYMPTOMS (Kemp)

Interval in years after infection to development of clinical neurosyphilis		
No treatment	Early inadequate treatment	Early adequate treatment
17 6	11 6	11 4

TABLE 80

THE EFFECT OF TREATMENT ON THE INCUBATION PERIOD OF THE VARIOUS TYPES OF NEUROSYPHILIS (Hopkins)

Type of neurosyphilis	Interval in years between infection and appearance of symptoms when the patient	
	Received no previous treatment	Was treated prior to the development of neurosyphilis
Diffuse meningovascular	13 9	10 4
Tabes	24 0	14 6
Paresis	19 5	15 3

The influence of race and sex upon the development of neurosyphilis —The influence of race and sex upon the course of syphilis has already been discussed in Chapter III. Their influence upon the develop-

ment of neurosyphilis is sufficiently striking to be worthy of further amplification. As shown in Fig. 57, among white males the incidence of clinical neurosyphilis alone is greater than the incidence of both asymptomatic and clinical neurosyphilis in white females. Negro males fare appreciably better than white females, while among Negro females clinical neuro-

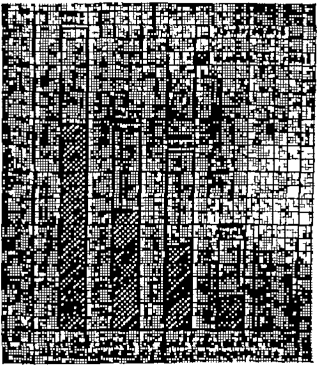


FIG. 57

syphilis is relatively uncommon and the total incidence of neurosyphilis is much smaller than in the other three groups.

The Prophylaxis of Neurosyphilis

A consideration of these facts and of the data as to asymptomatic neurosyphilis indicates that neurosyphilis is in part preventable. Among recognized syphilitics the 25 per cent expectancy of its development in untreated patients may be reduced by means of routine spinal fluid study appropriate intensification of treatment in those patients with abnormal fluids (in either early or late syphilis) and the use of fever therapy in patients who are serologically resistant to other measures to a probable 5 per cent or less Since the chance of "curing" clinical neurosyphilis once it has developed or even of obtaining complete symptomatic relief is nowhere nearly so great as this, the adage that an ounce of prevention is worth a pound of cure is obviously applicable.

Unfortunately, there is a barrier to the elimination of neurosyphilis more serious than the resistance to treatment of certain patients with recognized asymptomatic neuraxis involvement. This barrier rests on the fact that in many neurosyphilitic patients it is impossible to apply the prophylactic effect of treatment because the patient is unaware of his infection until neurologic symptoms appear Involvement of the nervous system is especially prone to occur in patients whose early lesions were so insignificant as to escape recognition or indeed in those with no early lesions at all, examples of symptomless infection. Likewise, neurosyphilitic patients are relatively unlikely to have suffered from benign late lesions of skin or bone which might have led them to a physician. These statements apply particularly to parenchymatous neurosyphilis (tabes and paresis) The majority of patients with these two grave forms of neurologic involvement can give no history either of obvious early or late lesions of syphilis and are totally unaware of the fact that they are infected until disaster overtakes them. The infected but unrecognized syphilitic is the huge and nearly untouchable reservoir of neurosyphilis. The only solution of this problem which occurs to us is the determined effort by physicians to recognize syphilis by means of routine serologic tests of patients reporting for any medical complaint, and particularly by means of the examination of contacts of patients known to be infected. When routine serologic tests reveal the diagnosis of syphilis routine lumbar puncture will reveal the possible liability to neurosyphilis.

The examination of the families of neurosyphilitic patients —This subject assumes special importance because of the clinical evidence pointing to a neurotropic strain of treponeme. It was long ago observed that several individuals infected from a single source might all develop neurosyphilis and that conjugal neurosyphilis was relatively frequent. Numerous observers have studied the latter point in detail, in this country particularly the Solomons Moore and Kemp The marital partners—husband or wife—of patients with parenchymatous neurosyphilis (tabes or paresis) have been found twice as liable to suffer from neurosyphilis as an unselected group of syphilitics. This is not true of the spouses of patients with diffuse meningovascular neurosyphilis the incidence of conjugal infection is high, but neurosyphilis among the infected spouses is not more frequent than among a control group.

The practical bearing of these facts is that the examination of the husband or wife of a neurosyphilitic patient is not complete unless in addition to a serologic test, a careful physical and neurologic examination is also performed and, in the event of the existence of the slightest suggestion of neurologic abnormality routine examination of the spinal fluid also even though the blood tests may be negative. In fact, in the case of spouses of paretics and tabetics we feel that lumbar puncture should be an obligatory routine even if all other findings are negative. In four wives of paretic patients we have found positive spinal fluids when all other examinations revealed nothing.

Among the syphilitic children of neurosyphilitic parents, too the incidence of congenital neurosyphilis is significantly higher than among an

unselected group of congenital syphilitics (Kemp and Poole) Routine lumbar puncture is not necessary in the children of such parents however unless clinical evidence of congenital syphilis or a positive serologic test is present.

The Prognosis of Neurosyphilis

The form of neurosyphilis which most uniformly kills is general paresis. Before the advent of fever therapy this disease was almost uniformly fatal within an average period of time dating from the onset of paretic symptoms, of 2 years. Vascular neurosyphilis also leads to ultimate death in a high proportion of affected individuals. Other types of late neurosyphilis including tabes dorsalis and late meningovascular involvement, are much less frequently immediate causes of death though they are often responsible for chronic invalidism and permanent incapacity It is first necessary therefore to consider the probability of development of paresis and its prognosis under different sets of treatment circumstances. In the prearsphenamine era it was estimated that about 5 per cent of all infected individuals untreated or treated with mercury alone would ultimately develop paresis. This has been further clarified by modern knowledge.

It is now possible to state with almost absolute definiteness that a patient with early syphilis whose spinal fluid is normal at the end of the probationary year following treatment (unless in the event of subsequent generalized relapse) or one with late syphilis (of more than 4 years' duration) whose fluid is normal before, during or after treatment, will never develop paresis (or tabes dorsalis) The ultimate victims of those two diseases come from the ranks of the patients with early involvement of the neuraxis, symptomatic or asymptomatic. What is their outlook for the future under the two circumstances of no or inadequate treatment and of adequate treatment?

The prognosis of asymptomatic neurosyphilis —Much practical information in this respect may be gained from a correlation of the type of spinal fluid change with the ultimate outcome. (For a discussion of the classification of asymptomatic neurosyphilis and the incidence of the three groups in early and late syphilis, the reader is referred to Chapter XXI.) This is probably best illustrated by tracing the course of the development of neurosyphilis in untreated patients, as schematically shown in Fig. 58. Invasion of the neuraxis occurs in every individual who contracts syphilis. In 60–65 per cent, however spontaneous regression occurs to the point that infection is not detectable clinically or serologically and, no matter what else may happen later these individuals do not develop clinical neurosyphilis. In the majority of instances this regression occurs early in the course of the infection. A small proportion of cases (0.3 per cent) however will develop clinical evidence of acute meningeal neurosyphilis, within a comparatively short time after infection (the rôle of treatment in precipitating this complication will be discussed later), and of these the majority will (if untreated) years later develop paresis In the remaining 30–35 per cent, infection of the neuraxis becomes asymptomatic and remains so for varying periods the length of time depending

upon the type of clinical neurosyphilis the individual is predestined to develop. Excluding purely vascular neurosyphilis, which as a rule develops earlier than the other types of late clinical neurosyphilis and which, as we have already pointed out, may be a manifestation of generalized involvement of the vascular system, it is possible from the results of the examination of the spinal fluid during this asymptomatic period to predict fairly accurately the type of clinical neurosyphilis a patient will ultimately develop If the findings in the cerebrospinal fluid are minimal, or

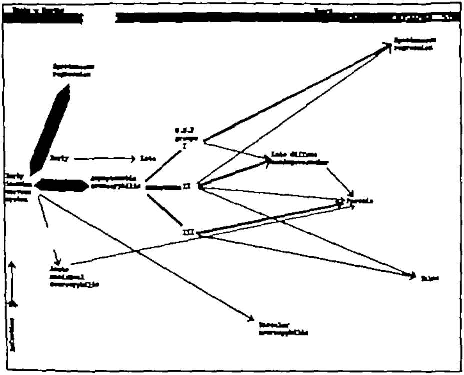


FIG. 58.—Schematic Representation of the Pathogenesis of Neurosyphilis. The horizontal block column at the top of the figure represents passage of time; the hiatus is intended to cover the transition period between early and late syphilis (about 4 years) Assuming that invasion of the nervous system occurs early in all persons infected (left of the figure) the width and direction of the arrows are intended to represent the approximate proportion of patients who reach a given end point (so far as the nervous system is concerned) and the approximate time at which the result is achieved. The course of events as portrayed is in untreated patients.

Group I (cf. page 346) spontaneous regression may be expected in the majority of instances. Late diffuse meningovascular neurosyphilis is the fate of the remainder If the spinal fluid changes are more marked, i.e. of Group II spontaneous regression occurs only occasionally the majority of patients developing meningovascular neurosyphilis and a few paresis or tabes. If however the spinal fluid formula shows maximum changes,

spontaneous regression rarely if ever occurs and parenchymatous neurosyphilis particularly paresis is the ultimate fate of all. There is no essential difference in the patient's final status whether these changes are discovered early or late in the infection. The time after infection when these various types of neurosyphilis become clinically evident varies within the time limits roughly indicated in Fig 58.

An approximate percentage estimate of the probable outcome of treatment, based on the findings of Moore and Hopkins in 109 patients, is presented in Table 81 With poor treatment, few patients of either group

TABLE 81

THE ULTIMATE PROGNOSIS IN ASYMPTOMATIC NEUROSYPHILIS (EARLY OR LATE)

Type of spinal fluid abnormality	Type of treatment	Approximate percentage of patients ultimately developing		
		Clinical and serologic "cure"	Parenchymatous neurosyphilis (tabes and paresis)	Meningovascular neurosyphilis
Moderate (Group II)	Adequate	90–100	1–2	3 5
	Inadequate	10–25	5–10	65–85
Intense (Group III–the paretic formula)	Adequate	60–80	10–30	5–10
	Inadequate	5–10	70–80	10–20

remain well with good treatment, the prospect of ultimate "cure," both clinical and serologic, is much better in patients with Group II fluids (90–100 per cent) than in those whose fluids show the paretic formula (60–80 per cent) As pointed out before patients with Group II fluids tend *overwhelmingly to develop meningovascular neurosyphilis those with* Group III fluids parenchymatous neurosyphilis (and of these, preponder antly paresis rather than tabes) With poor treatment, 70–80 per cent of

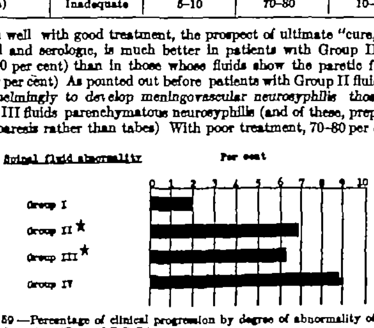


FIG 59—Percentage of clinical progression by degree of abnormality of spinal fluid on detection. (Data of C.C.G)

★ These groups (II and III) of the C.C.G correspond to Group II as used throughout this text.

Group III patients may ultimately be expected to develop paresis or tabes even with the best available treatment methods including fever therapy this catastrophe may occur in 10–30 per cent. Although the data of the C.C.G (Fig. 59) do not lend themselves to such a detailed analysis they are in general agreement with the above findings of Moore and Hopkins

The prognosis of early acute meningeal neurosyphilis —Until recently little was known of the ultimate fate of patients with early acute meningeal neurosyphilis (including neurorecurrence) Because of the absence of a history pointing to this type of involvement in most paretics it was even assumed that acute syphilitic meningitis might actually protect the patient against the subsequent development of paresis Studies from the Johns Hopkins clinic and by Rothschild and Merritt and Moore have shown however that the reverse is the case, and that the significance of early meningeal neurosyphilis for the patient's future is as grave as that of asymptomatic neurosyphilis. The data of these three series are combined in Table 82, again dividing the patients on the basis of adequate

TABLE 82

THE FINAL STATUS IN 91 CASES OF ACUTE SYPHILITIC MENINGITIS

Series reported by	Good Treatment				Poor Treatment			
	Recovered	Tabes	Developed paresis	Other types	Recovered	Tabes	Developed paresis	Other types
Rothschild	20	0	0	0	3	3	3	2
Moore, J E.	10	0	2	2	7	0	1	6
Merritt and Moore	21	0	1	3	1	1	1	4
Total	51	0	3	5	11	4	5	12

and inadequate treatment. With adequate treatment after the development of the lesion 86 per cent of patients may be clinically and serologically "cured" with poor or no treatment, only 34 per cent. Nearly a third of the poorly treated patients develop paresis or tabes usually the former and an even larger proportion late meningovascular neurosyphilis Even with thorough treatment, these accidents cannot be entirely prevented, though their incidence is enormously reduced.

The prognosis of general paresis —Numerous studies are available as to the ultimate fate of paretic patients. We utilize particularly the reports of Tophoff and of Raynor dealing with 1,300 patients who received no treatment, of Furman reporting on 500 patients treated with routine pre-malaria methods (arsphenamine and the heavy metals) and of many investigators who have summarized their experiences with malaria. These data are shown in Table 83.

spontaneous regression rarely if ever occurs and parenchymatous neurosyphilis particularly paresis is the ultimate fate of all. There is no essential difference in the patient's final status whether these changes are discovered early or late in the infection. The time after infection when these various types of neurosyphilis become clinically evident varies within the time limits roughly indicated in Fig 58.

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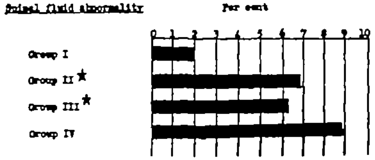


FIG. 59 —Percentage of clinical progression by degree of abnormality of spinal fluid on detection. (Data of C C.G)

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With adequate treatment, symptomatic relief and complete arrest of progress is attainable in about 80 per cent of patients in this group.

The prognosis of vascular neurosyphilis.—The immediate prognosis of a more or less purely vascular neurosyphilis is relatively good, certainly much better than in cerebral vascular accidents due to other causes. Recovery from paralysis may be partial or complete. If it occurs it is usually fairly prompt, i.e. within several months. Unfortunately, however, and with or without treatment, the neurosyphilitic patient who has once suffered a cerebral thrombosis or hemorrhage is prone to develop subsequent similar accidents, even though the interval between them may be many years. The risk of permanent incapacity or death is greater than in the more diffuse type of meningovascular neurosyphilis.

The prognosis of tabes dorsalis.—Except from sphincter paralysis, the development of cord bladder, and ascending urinary infection, tabes is rarely a direct cause of death. It is often, however, a cause of the most distressing chronic invalidism and permanent incapacity, partial or complete. In order of frequency, the particular manifestations of the disease responsible for incapacity are lightning pains, cord bladder, ataxia, gastric crises, Charcot joints and optic atrophy. Lacking the influence of treatment, it is safe to say that 90 per cent of all tabetics will be handicapped by one or other of these symptoms, the degree of incapacity ranging from the relatively minor inconvenience of periodic bouts of mild lancinating pain to bed-ridden ataxia, to the pain and nausea-wracked agony of nearly constant gastric crises, or to complete blindness. In a few instances, the disease seems spontaneously to "burn out" after producing enough damage to cause the appearance of mild symptoms and typical physical signs; progress is, for some unknown reason, stayed and the patient remains in *status quo* for many years. These fortunates comprise no more than 10 per cent of the total.

So far as the effect of treatment is concerned, the outlook depends on the extent to which inflammatory lesions are replaced by degenerative processes at the time treatment is begun. In the individual case it is usually impossible accurately to evaluate these two factors. One would expect the obviously degenerative manifestations, such as optic atrophy and Charcot joints, to make the poorest therapeutic response, and such is the case. Surprisingly, however, tabetic bladders, which are usually considered as due to cord degeneration, are frequently restored to good function following treatment. On the other hand, lightning pains and gastric crises, which are thought to be caused by inflammatory lesions, may be entirely resistant to treatment. To measure the effect of treatment in tabes, more than in any other type of neurosyphilis, is to speak in terms of relief of particular symptoms rather than of the disease picture as a whole. The C.C.G. have provided such an analysis in 1,507 cases of tabes (Figure 60), considering all modern methods of treatment except fever therapy. In most respects our experience is in accord with theirs; with certain symptoms, particularly optic atrophy, our results have been more encouraging (Chapters XX and XXIV).

Considering the disease process as a whole, the results of treatment in

tabes are less satisfactory than in any other type of neurosyphilis except paresis Complete symptomatic relief prolonged serologic negativity and permanent arrest of progress are securable in only about 30–40 per cent of patients treated.

The prognostic import of the paretic formula in the spinal fluid —In most patients with general paresis the abnormalities in the spinal fluid are strikingly uniform moderate pleocytosis marked excess of protein strongly positive Wassermann (with 0 1 cc or less) and first zone (paretic) colloidal curves. This type of spinal fluid deserves the name paretic formula Although it almost always occurs in paresis it is by

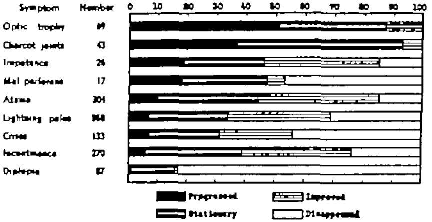


FIG. 60 —Percentage of Clinical Response to Treatment of Symptoms of Tabes (From C.C G.)

no means diagnostic of this condition since it occurs in other types of neurosyphilis symptomatic as well as asymptomatic early as well as late In repeated publications Moore has stressed the fact that this type of fluid abnormality especially if treatment efforts fail to effect significant improvement is of serious prognostic import. It indicates definitely that the patient is in danger of developing further neurologic progress which is particularly likely to be tabetic or paretic in nature

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Chapter XXIII

THE TECHNICAL ASPECTS OF TREATMENT OF NEUROSYPHILIS FEVER THERAPY, TRYPARSAMIDE, SUBDURAL TREATMENT

Before proceeding to a discussion of treatment of individual types of neurosyphilis it is essential first to supply information as to certain theoretical considerations particularly pertinent, and to describe in detail certain specially applicable forms of treatment not heretofore considered in detail.

The permeability of the blood spinal fluid barrier in relation to treatment —It is an old observation that most foreign substances, e g. bacteria, dyestuffs antibodies and drugs introduced into the blood stream do not penetrate into the central nervous system at all or penetrate only in small quantities. There is interposed a barrier which under ordinary circumstances keeps such substances out. In syphilis, unfortunately the hemato-encephalic barrier does not effectively exclude the treponeme from the nervous system, though it does largely exclude the various antisyphilitic drugs used to attack the organism which can be found in cerebrospinal fluid or nervous tissues only in very low concentration. It is generally assumed that this is one of the most important reasons for the relative lack of success of treatment in neurosyphilis as contrasted to syphilis of the other organs.

However it has been shown by various workers that the permeability of the barrier is increased not lowered in the presence of acute or chronic inflammatory lesions. In patients with various types of neurosyphilis drugs and dyestuffs penetrate the nervous system more readily than in normal individuals. Furthermore as the symptoms of neurosyphilis improve as a result of treatment, permeability may decrease (Malamud and Wilson) Attempts have been made to increase the permeability of the meninges to drugs by such procedures as jugular compression decreasing the spinal fluid volume by spinal drainage the intravenous injection of *hypertonic solutions (saline or glucose) and the setting up of an aseptic* meningitis and to explain the results obtained in neurosyphilis on this basis Much of the work done is conflicting in results and not directly applicable to practice by the physician. For the time being opinion as to the importance of the barrier in antisyphilitic treatment must be withheld. It is not yet clearly demonstrated for example, that the concentration of drugs in a given tissue is the factor directly responsible for improvement of a lesion of that tissue. Indeed certain of the experiments with bismuth (Levaditi and his associates) would suggest that this is not necessarily true Until this fact is proved it seems to be only of academic importance to lay stress on the concentration of drugs in the spinal fluid of treated patients or on the adoption of methods calculated to increase their concentration.

This whole subject is a complicated one, demanding familiarity with the physiology of the spinal fluid and with the experimental investigations on the encephalic barrier The interested reader is advised to consult the publications of Weed and his associates, Fremont-Smith and Kafka.

Fever Therapy

Wagner von Jauregg deserves full credit for the introduction of a new and effective method into syphilotherapy He and others before him had observed that patients with various psychoses including paresis sometimes improved after a febrile illness. His original observations were made in 1887 For the next 30 years he tried one method after another of inducing fever in paretic patients—deliberate inoculations with erysipelas, treatment with tuberculin with vaccines of various sorts with sodium nucleinate. The results while not startling, were sufficiently good to prompt further effort. Finally in 1917 he hit upon the idea of deliberate inoculation of paretic patients with tertian malaria. In that year 9 patients were treated, of whom 4 promptly developed complete remissions (two of these patients were still well at the date of last reporting, 20 years later) These results prompted the wide-spread use of malaria as treatment for paresis, with prompt confirmation of the original favorable report. Detailed studies made in Wagner von Jauregg's clinic and elsewhere, were collated in 1925 and 1928 by von Jauregg's associate Gerstmann. Still more recent monographic discussions are provided by Rudolf and by Dattner

Prompted by the favorable results of malaria therapy in paresis more recent investigations have taken two forms —attempts to benefit by induced fever other forms of neurosyphilis than paresis and indeed to extend its use to syphilis in general and efforts to discover other methods of inducing fever which might be equally efficacious and less troublesome or dangerous than malaria. In this search, trials have been made of the effect of relapsing fever rat-bite fever protein shock hot baths diathermy electric blankets fever cabinets and short-wave radio An enormous literature has grown up around the subject, too vast for complete review Here only a summary will be attempted in which credit for original observations will often be omitted.

TYPES OF FEVER THERAPY

- Malaria, tertian
- Malaria, quartan
- Mechanical fever
  - Air conditioning
  - Electropyrexia (diathermy short-wave radio)
- Protein fever
  - Typhoid vaccine

FIG. 61

Experimental Observations on the Effect of Fever in Syphilis

Malaria had not been long in use before attempts were made to determine the effect in experimental rabbit syphilis, of the most obvious feature of malaria therapy fever The results of these investigations are confusing and contradictory Weichbrodt and Jahnel who first studied the problem, found that the exposure of rabbits with scrotal chancres to an incubator temperature of 41°C (105.8°F) with the resultant elevation of the animals' rectal temperature to heights ranging from 42–45°C (107 6–113°F) caused more prompt regression of lesions and disappearance of surface organisms than in control animals. Schamberg and Rule demonstrated that repeated exposure of syphilitic rabbits to hot baths at a temperature of 42°C (107 6°F) had both a prophylactic and curative effect. These results could not however be completely confirmed by Frazier working in Chesney's laboratory Later Kolmer found that the prophylactic effect of heat depended on its local application to the inoculated testicle, rather than on general elevation of body temperature. Kolmer's results have been confirmed by Bessemans. In contrast, Levaditi has found that a large percentage of rabbits with active testicular syphilomas could be cured as judged by lymph node transfer by fever (diathermy) even though the temperature of the inoculated testicle did not reach the assumed thermal death point, 41–42°C. (105 8–107 6 F) of the treponeme. In a series of analogous but not exactly parallel experiments Bessemans confirmed Levaditi's findings. Bessemans found also that temperatures which killed treponemes in more superficial structures did not immediately destroy them in the popliteal lymph nodes of rabbits Later however the nodes became sterile without further treatment. These experimental observations by Levaditi and Bessemans, and the important clinical observations by Neymann and his co-workers that during hyperpyrexia all tissues in the body do not share to the same extent in the elevation of temperature support the assumption of most fever therapists that the beneficial effect of fever particularly in the treatment of neurosyphilis depends upon some factor or factors other than the rise in temperature. What in addition to the fever is responsible is not evident at present from either clinical or experimental observations.

Most observers (Boak Carpenter and Warren Neymann and Lawless, and Bessemans) agree that the treponeme has a relatively low thermal death point and that either *in vivo* or *in vitro* it is destroyed by temperatures of 42°C (107 6 F) maintained from 1–6 hours. It is on the basis of these observations that a wide variety of fever producing agents has been tried in human therapy Their place in the hyperpyrexial treatment of neurosyphilis will be discussed later in this chapter

The Physiology and Pathology of Fever

The considerations which follow have largely developed from studies of fever produced by physical means (Krusen and others) but in large part apply also to fever due to disease (malaria)

A maximum temperature of 42°C (107 6°F) may be safely tolerated

by robust adults for a period of 4 hours but this level should never be exceeded and is too high for many neurosyphilitic patients Pulse and respiration increase in proportion to the temperature. During fever the systolic blood pressure rises the diastolic falls often to very low levels the latter due to extreme peripheral vasodilatation. Between paroxysms of fever both systolic and diastolic pressures fall below their usual levels. The velocity of blood flow is increased blood volume is decreased.

In paroxysms of mechanically induced fever and during defervescence in malaria there is profuse sweating with excessive chloride excretion. During electropyrexia, blood nonprotein nitrogen, uric acid, sugar, protein content and electrolytes increase due to concentration of blood volume though in malaria the prolonged increase in blood nonprotein nitrogen sometimes observed is hardly explainable on this basis. The metabolic rate rises during fever the blood lactic acid also rises, and there may be mild acidosis. The urine volume is decreased, specific gravity increases and transitory albuminuria and cylindruria occur

Delirium may appear as the temperature reaches about 38 9°C. (102°F) and is a constant accompaniment of the rare and unfortunate instances of hyperpyrexia. In patients and animals studied pathologically after fever to ordinary therapeutic levels no striking tissue alterations are demonstrable but in those dead after hyperpyrexia, there are extensive hemorrhages and necrosis of muscles liver kidney lungs, adrenals heart, and brain (Hartman)

Indications for Fever Therapy

Paresis, taboparesis and primary optic atrophy are imperative indications for the use of fever The results are so much better than with any other form of treatment that to postpone fever in favor of a trial of other methods is to invite progressive mental deterioration and death, or blindness. Results are less satisfactory in far advanced rapidly advancing (galloping) and in juvenile paresis than in other forms but paresis and primary optic atrophy are such otherwise hopeless diseases that it pays to take risks relying on the experience of the physician should complications arise.

In other types of late neurosyphilis fever may be a method of election or of necessity In general since fever therapy carries with it more of a risk to life than the arsphenamines, mapharsen, tryparsamide, and the heavy metals it is our custom to reserve it until lack of clinical improvement or prolonged serologic resistance indicates its desirability In the average patient (excepting paretics and patients with optic atrophy) this means at least a year of preliminary treatment, employing first the trivalent arsenical drugs and heavy metals, then tryparsamide, before fever is advised. In many patients with late syphilis however and especially those with the paretic formula in the cerebrospinal fluid, fever may be undertaken earlier on the grounds that it improves the patient's chance of prolonged clinical improvement and that it shortens the time of treatment, thereby lessening expense. One may accomplish as much, we believe with fever plus a subsequent 12–18 months of chemotherapeutic treat

ment as with three years of chemotherapy alone and while the expense of fever is condensed within a few weeks the total cost of treatment will be less if it is used. More is said of this under the specific headings of treatment of various types of neurosyphilis.

In early neurosyphilis (acute meningeal or asymptomatic) fever should be withheld until the patient has received at least a year of arsphenamine and heavy metal, for its general treponemicidal effect. In treatment-resistant syphilis, fever therapy is also particularly indicated (see Chapter XIII)

In any case the patient s general physical condition should be good. Advanced age marked undernutrition, active pulmonary tuberculosis obesity, aortic aneurysm are temporary or permanent contra-indications. Syphilitic aortitis is not a contra-indication even in the presence of compensated aortic regurgitation though such patients require special cardiac supervision during treatment.

Fever by Induced Malaria

The following summary is drawn in part from Gerstmann s monograph, in part from more recent significant contributions to the literature and in part from experience in the Johns Hopkins clinic with about 1 600 treated patients.

Source of malaria —Benign tertian malaria is the infection of choice Its clinical manifestations are less severe and it is more readily controllable with quinine. Although the infection may be carried in the laboratory in mosquitoes (Boyd) direct patient to patient transfer is much simpler Under these conditions it is preferable to employ only a strain previously carried on in a large clinic where its tertian nature has been proved by repeated human passages. If it is necessary to utilize a patient with natural malaria as a donor it is essential (1) to reject any donor who may have been in the tropics* (even the absence of organisms is no proof of freedom from tropical malaria) and (2) to carry out frequent preliminary examinations of the donor's blood in thick and thin smears by a competent observer in order to verify the presence of *P vivax* and the absence of other parasites

The danger of accidental inoculation with tropical (aestivo-autumnal) malaria is a real one. Numerous instances of death have been reported in patients in whom this type of organism was purposely or accidentally injected.

Recently quartan malaria has been used extensively in treatment (Kirschbaum Fong and in our own clinic by Kroll) Its field of special value is for second attacks of fever in patients already once treated with tertian malaria and immune to reinoculation in debilitated patients (since its course is milder than that of tertian malaria) and in Negroes who are refractory to inoculation with the tertian strain almost in direct proportion to skin pigment. Fong reports that only about 55 per cent of Negroes are susceptible to inoculation with the quartan strain but in our

* We have recently discovered *Filaria bancrofti* in the blood of a patient with tertian malaria proposed as a tentative donor The patient had been in Africa.

own experience only 5 of 46 Negro patients were refractory Several observers (Branche, Kroll, and Fong) have reported satisfactory clinical results in both Negro and white patients, and Mays Oden and Cox think that in the treatment of general paresis it is superior to tertian malaria.

Ape malaria (plasmodium Knowlesi) first suggested by Van Rooyen and Pile and extensively tried by Ciuca and by Milam and Kusch, apparently possesses no particular advantage over the tertian or quartan strains. In addition to the disadvantages of running a very irregular course with a tendency to spontaneous remission it is occasionally dangerously invasive and frequently relapsing Negroes are not susceptible to it.

There seems to be no difference in therapeutic effect with various strains of tertian malaria nor in spite of frequent human transfers (with the omission of that part of the life cycle which occurs in the mosquito) any noteworthy alteration in the duration of incubation period the height or character of the fever or the morphology or pathogenicity of the plasmodium.

There is no danger of transmitting syphilis (superinfection) by means of the inoculation of one neurosyphilitic patient from another So far as is known treponemes are not present in the blood stream of patients with late neurosyphilis As a matter of fact, there is probably no great danger of transmitting syphilis even to a non-syphilitic person by means of inoculation with malarial blood of patients with late neurosyphilis, though the esthetic objections to this procedure are great enough to prevent it.

The technique of inoculation —Various routes of inoculation may be used e.g., intradermal subcutaneous intramuscular or intravenous. The incubation period varies with the route chosen longest with intradermal, shortest with intravenous * It is also said that the course of the subsequent malaria tends to be more purely tertian after intradermal inoculation while it is usually irregular and finally quotidian after other routes. The intravenous route is the one in common use the size of the inoculum varying from 1–10 cc. (dangerous to give more than 10 cc. if unmatched blood is used) It is best when using this route to employ matched blood whenever possible. This not only avoids the sharp immediate febrile reaction which frequently follows the use of unmatched blood but, according to Polayes and Derby when the donor's blood is compatible the incubation period of malaria in the recipient is much shortened and the temperature response is much more satisfactory We can confirm the observation as to shortened incubation period.

* In Great Britain patients are usually inoculated by the bite of infected mosquitoes (Yorke and MacFie) This is, we believe, not only unnecessary but, unless selected strains are used, may also be undesirable because such infections are sometimes less susceptible to quinine and more prone to subsequent relapse than the variety induced by direct i oculation. In this country it has been proposed (Mayne) that malaria be induced by the intravenous injection of the macerated salivary glands of infected mosquitoes. It has also been shown by Boyd and by Stoll and his associates that malaria may be transmitted by the bite of infected mosquitoes kept in the laboratory The suggested advantage is that mosquitoes may be more easily shipped from place to place than infected blood The same objections apply to this method as to the British practice

If donor and recipient are in the same or adjoining rooms so that the inoculation may be made with whole blood before clotting occurs it is necessary only to have the arms of both patients cleaned up with iodine and alcohol, to withdraw a *few* cc. of blood from the donor to change the needle to a fresh sterile one, and to inject the blood immediately into the recipient. If the distance between the two patients is so great that more than a minute must elapse between bleeding and injection the blood must be kept from clotting by citration This does not impair the vitality of plasmodium. Sodium citrate, 2 5 per cent, is drawn into the sterile empty

MALARIA ROUTINE

Inoculum—donor and recipient side by side, whole blood.
Recipient distant, citrated blood (1 cc. 2.5% citrate to 10 cc. blood)
Blood may be kept 12–24 hours in icebox, room, or incubator
Blood may be drawn from donor at any time relative to paroxysms.
Risk of superinfection with syphilis—none!
Matching unnecessary

Inoculation—intravenous, 5–10 cc. *slowly* Watch for immediate and delayed transfusion reaction.

Incubation period—tertian 1–14 days (average 6) quartan 10–60 days (average 21)
May be shortened by
route of inoculation (intravenous shortest)
matching of blood
size of inoculum.

FIG. 62

syringe, in the amount of 1 cc. for each 10 cc. of blood to be withdrawn and is mixed with the blood in the syringe. This citrated blood may then be placed in a sterile flask or test-tube and transported to the recipient.

It is of no importance, so far as the infectiousness of the blood is concerned at what point in the donor's paroxysm blood is withdrawn Inoculations are equally as successful in the apyrexial period as at the height of the fever There is however some influence on the incubation period, which will be a day or two less if the inoculum is withdrawn just before the beginning of a paroxysm at a moment when merozoites are free in the circulating blood and capable of penetrating the recipient's red cells at once.

Susceptibility and non-susceptibility to malaria—In white patients who have never previously had malaria (natural or induced) intravenous inoculation usually induces the disease. If the first inoculation does not take (about 7 per cent of instances) a second utilizing 10 cc. of blood intravenously will almost always be successful. In the Vienna clinic, only 5 of 1 000 attempts were failures

In white patients who have previously had natural malaria at any time or induced malaria within certain fairly definite time limits (see page 388) attempts at inoculation by any route and with any amount of blood are usually failures. Curiously enough, although there is no evidence of natural immunity in the white race, this phenomenon appears to exist as to tertian malaria among Negroes about half of whom cannot be successfully inoculated, regardless of whether or not they have previously had the disease. Curiously also this racial immunity does not extend to the quartan parasite, to infection with which Negroes are usually susceptible.

Certain individuals who appear to be refractory to inoculation with unmatched blood may be successfully infected if a donor is used of the same blood group as the recipient (Herrmann and Hlesnikowski Wendlberger) Under these circumstances (matched blood) infection can be induced by the administration, if necessary of a very large inoculum (as in our experience in several patients, 50–200 cc.) This procedure has the additional advantage of shortening the incubation period, in some instances to as little as 24 hours.

The conservation of infectious malarial blood —Since it is often difficult to transport patients to malaria, it is necessary to be able to transport malaria to patients. Citrated blood (1 cc. of 2.5 per cent sodium citrate to 10 cc. blood) will remain infectious at icebox, room or body temperature for 12–48 hours during which time it may be shipped by air mail in sterile containers. To ensure its infectivity it is important to bleed the donor at the height of or immediately after a paroxysm at which time young resistant forms predominate in the blood. Horn and Kanders have devised a more complicated method of maintaining the infectiousness of blood over a period of 92 hours but today with a strain of malaria available in every large city this is no longer necessary

Examination of the blood for plasmodiae —Parasites may sometimes be found in small numbers even during the incubation period, but always after the first frank paroxysm.* The course of the fever is not in direct relationship with the stage of development of the parasites which as a matter of fact develop irregularly Young schizonts (ring forms) amoeboid and more mature forms may be found side by side in the same smear This explains the irregularity of the early febrile paroxysms. As compared with the natural infection plasmodiae are relatively rare and less rich in pigment.

Asexualization of the plasmodium —When malaria is reproduced by direct passage from patient to patient, eliminating the natural vector the mosquito the tendency to produce sexual forms of the parasite (gametocytes) gradually disappears (in one strain studied by Kopeloff and his associates, about 2½ years were required for this phenomenon) This is of practical importance, since when only a sexual form of the parasite is present in the patient's blood development of the full life cycle will not occur in the mosquito and screening of the bed is not necessary

* Dattner states that in pregnant women plasmodiae may pass the placental barrier and be found in the fetal blood.

The length of time required for complete disappearance of gametocytes probably explains the differences of opinion between the Vienna and the British schools as to the transmissibility of induced malaria by mosquitoes (Gerstmann Yorke and MacFie) The asexual development of the tertian parasite is possibly also a reason for the relatively benign course of induced as compared with natural malaria. There is as yet little information concerning the asexualization of induced quartan malaria, though since the intermediate mosquito host is also eliminated presumably the same train of events occurs

Incubation period of induced tertian malaria —When blood is given intravenously the average incubation period is 3–8 days with extremes of 1–20 days Generally speaking the larger the inoculum the shorter the incubation period. If there is no sign of a take within 10 days, it is our usual custom either to attempt the provocation of an attack with adrenalin given intramuscularly or with a small dose (50–100 million or ganisms) of typhoid vaccine given intravenously or to reinoculate the patient with fresh infectious blood.

The course of tertian malaria —During the incubation period there are usually no symptoms. After a few days there often appears a low-grade irregular fever ranging up to 37 7–38.3°C (100–101°F) To-

MALARIA ROUTINE

During incubation period

1 Watch for immediate short rise in temperature if blood unmatched.
2 Patient may carry out usual activities, or if in hospital, need not be in bed.
3 Temperature (mouth) q. 4 h. while awake.
4. When temperature reaches 101°F complete bed rest.

FIG. 63

ward the end of the prodromal period this fever may attain considerable height and it is often difficult accurately to define the first paroxysm.

After two or three days of irregular fever there is a sharp rise, characteristic of the typical tertian paroxysm. The first few paroxysms are usually irregularly spaced and throughout, the course is atypical as compared with the natural disease. Purely tertian chills are relatively rare in most patients the paroxysms appear as quotidian. The typical attack starts with a sharp shaking chill and a rapid rise in temperature to 40–41 1 C (104–106°F) (rarely to higher levels) After remaining at this height for 1–3 hours there is a gradual fall to normal, occupying about 12 hours and during which there is profuse sweating. Subjective symptoms are malaise severe headache anorexia, and exhaustion Although the height of the peak of fever has little apparent relation to the therapeutic outcome the duration of the fever above 37 7°C (100°F) (optimum 150 hours at this level) is apparently important (Kopp and Solomon) indeed we and others

have seen excellent clinical results in paretic patients whose temperatures remained comparatively low

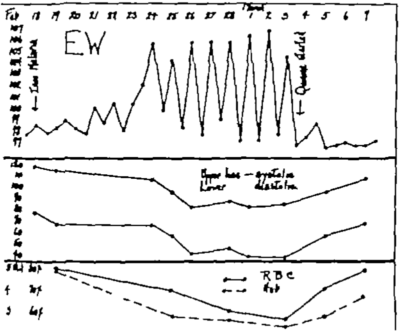


FIG. 64.—Specimen temperature curve during malaria therapy Note incubation period of 5 days after intravenous inoculation, prodromal fever before definite paroxysms begin, quotidian course, prompt subsidence after start of quinine, fall in blood pressure, rapidly developing and equally rapidly recovering anemia.

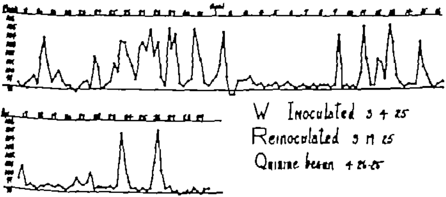


FIG. 65.—Specimen temperature chart during malaria therapy Note long incubation period (16 days) after intravenous inoculation, apparent failure of first inoculation to take, prompt rise in temperature 24 hours after second inoculation, complete irregularity of paroxysms with two long periods each of 8 days of spontaneous cessation of paroxysms, prompt subsidence after quinine.

To the average patient in good physical condition from 10–14 paroxysms are usually permitted. In counting paroxysms, the prodromal fever is not considered, and only those paroxysms are counted in which the temperature reaches an elevation of 39.3 C (103°F) or over. No attention is paid to the number of chills; an occasional patient will have repeated febrile paroxysms not preceded by a chill. If for any reason it becomes necessary to interrupt the malaria before the completion of the desired number of paroxysms reinoculation may be practised a few weeks later.

SPECIAL INDICATIONS FOR QUARTAN MALARIA

1. In Negroes.
2. In debilitated patients.
3. In those immune to tertian malaria.

FIG. 66

Apparently a minimum of 10 paroxysms is essential for therapeutic benefit, the probability of which is improved by additional paroxysms up to 12. There is little satisfactory evidence however that more than this is of added value (Ferraro and Fong; Kopp and Solomon).

MALARIA ROUTINE

During malaria

1. Complete bed rest.
2. T (rectal) P R q 2 h. while awake; q. 30 min. from start of paroxysm until defervescence begins.
3. For T 106 F + repeated tepid sponges.
4. B P 2 q d.
5. Support falling B. P with ephedrine or paredrine hydrobromide, digitalis if necessary.
6. For discomfort, codeine 32 mgms., aspirin 0.3 gm. p.r.n. not oftener than q 4 h.
7. NaCl gms. 6.0 q.d. during fever (to replace chlorides lost by sweat).
8. Examine urine q. 2 d.
9. Hgb., R. B. C. q 3–5 d.
10. N P N q 3–5 d.
11. Diet as desired. Urge patient to eat.

FIG. 67

The course of quartan malaria.—The quartan strain produces a much milder disease than the tertian and presents fewer and less severe complications. In some patients the paroxysms are purely quartan (at 72

hour intervals) in others, they may be completely irregular or even quotidian. The peak of temperature averages slightly lower than the tertian strain. Anemia, prostration, jaundice, and other sequelae are infrequent and mild.

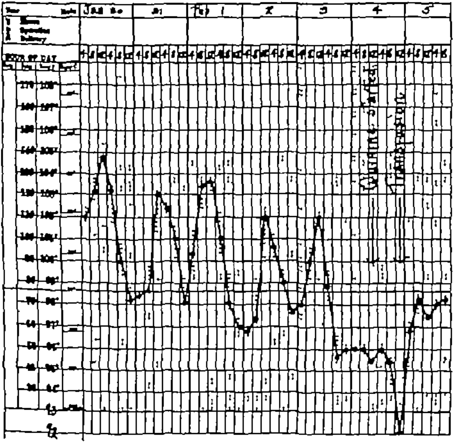


FIG. 68.—To show extreme fall in temperature in therapeutic malaria.

U 16302. White female, aged 39, with diffuse meningovascular neurosyphilis. The rectal temperature of 93°F verified by three thermometers, followed the sixth paroxysm of induced malaria. When the temperature was at its lowest point, the patient was in profound shock, cold, clammy sweat, thready pulse, blood pressure 65/48. Prompt recovery after transfusion.

The medical care of the patient during malaria Complications —As soon as the first elevation of temperature occurs, the patient should be put at complete rest. The rectal temperature should be taken every 2 hours while the patient is awake (at the beginning of a chill, half hourly until the temperature begins to drop, so as not to miss the peak) High temperatures (to 41.1 C [106°F] rectal) need occasion no alarm the extreme elevation is maintained only for an hour or so, and indeed,

within limits high fever is desirable. Temperatures over 41.1 C (106°F) may be promptly reduced, if desired by means of a tepid sponge repeated if necessary Death from hyperpyrexia is exceedingly rare We have seen a patient who in one paroxysm attained a rectal temperature of 42.2°C (108°F) without harm. In an occasional rare instance there are wide swings in temperature which falls during afebrile periods to 35 C (95°F) or less We have records of one patient in whom a rectal temperature of 33.3 C (92°F) was accompanied by the symptoms of profound shock, from which she was rescued by emergency blood transfusion.

Malaise headache the exacerbations of lightning pains in tabetics and of psychotic symptoms in paretics which are concomitants of fever may be controlled with sedative drugs. We usually employ codeine 32 mgms. and acetylsalicylic acid 0.3 gm. given together by mouth as necessary not oftener than every 4 hours. The slight antipyretic action of the coal tar drugs may be disregarded

The blood pressure should be taken twice daily Both systolic and diastolic pressures always fall the latter to very low levels and to a greater extent during febrile than during afebrile periods. The diastolic level may be ignored, but if the systolic pressure falls below 90 mm. of mercury supportive measures are desirable if it falls below 70 the malaria should be promptly interrupted, to prevent possible sudden cardiac failure. A second valuable sign indicating probable myocardial damage is marked tachycardia persisting during afebrile periods (pulse rate 120–140) This also is an indication for temporary or permanent interruption of the fever For falling blood pressure it is our usual custom to employ ephedrin by mouth four times daily in doses of 25–50 mgms and in most cases the simultaneous administration of powdered digitalis twice daily in 0 1 gm. dosage. Full digitalization is neither necessary nor desirable Though report of increase in toxicity of both digitalis and ephedrin by their combined use has been made (Johnson and Gilbert) we have seen nothing to indicate that this is true in the dosage in which we have employed the two drugs.

To compensate for the loss of chlorides through sweating with its consequences of exhaustion prostration and nausea it is essential to administer sodium chloride. This should be begun as soon as the temperature rises the salt may be given by mouth as enteric coated tablets 2.0 grams three times daily The intravenous injection of normal saline is rarely necessary The improvement in the patient's sense of well being during malaria as a result of salt administration is indeed striking

Hemoglobin estimation and erythrocyte counts should be made every third or fourth day Malaria causes a rapidly progressive anemia which however rarely arouses alarm and need not prompt interruption of the infection unless the hemoglobin falls below 7 1 grams per 100 cc. (50 per cent) At the conclusion of the malaria, no special measures such as the administration of iron compounds are necessary to facilitate recovery from the anemia, which is almost as prompt as was its appearance.

We have seen in three malaria-treated paretics granulocytopenia (leucocyte count 800–2000 granulocytes 10–35 per cent) persisting for

some days during quinine therapy it was accompanied by a day or two of otherwise unexplained fever, but not by necrotic angina or other constitutional symptoms. This alarming experience had not been previously encountered among some 600 malaria-treated patients. According to Schilling and his co-workers and Winfield, marked leucopenia is frequent during the actual course of induced malaria, usually disappearing promptly afterwards. Meyer and Jacobson and Abel have reported 4 cases of post-malarial agranulocytosis, one of which was fatal. In most instances, however, the prognosis seems to be good for gradual recovery without treatment. Nevertheless such patients should be carefully guarded against intercurrent infection, and we should hesitate to administer an arsenical drug until the leucocyte count had returned to normal.

Nausea and vomiting are not uncommon at the height of each paroxysm. In rare instances this may continue during afebrile periods. If it cannot be controlled by symptomatic treatment, the malaria must be interrupted to prevent rapid exhaustion, dehydration and starvation acidosis.

Jaundice, usually only faintly visible in the sclerae, occurs in about half the patients treated. It is mild and need not be feared. It is probably largely hematogenous in origin, from the rapid destruction of red cells by the plasmodium. Mülbradt, who has studied this question carefully, has found no permanent damage to the liver in 1 000 cases of malaria inoculata. In the few instances in which slight damage was detectable by liver function tests performed immediately after treatment, later tests were normal. On the other hand, in a rare patient, deep and progressively increasing obstructive jaundice may occur accompanied by enlargement and tenderness of the liver, bile in the urine and clay-colored stools. This is surely due to toxic hepatitis as a direct result of malaria. In the three or four such cases we have seen, we have regarded such severe jaundice as an indication for permanent interruption of malaria. Bruetsch, Materna and others agree that in some instances actual damage to the liver may occur with the eventual production of atrophic cirrhosis. Although we have seen at least one example of Laennec's cirrhosis developing some 12 years after therapeutic malaria, we are not convinced that there is any relationship between the two.

Almost uniformly the spleen becomes palpable as a hard, firm, rubbery, painless organ 2–4 cm. below the costal margin. In rare instances *spontaneous rupture of the spleen occurs. Eight cases gathered from the literature* and an additional one of their own have been reported by Polayes and Lederer. We have seen two examples in about 1 600 patients treated, though Dattner states that no cases have occurred in more than 5,000 patients treated in the Vienna clinic. This accident is completely unpredictable and unpreventable and is usually rapidly, sometimes almost instantaneously, fatal. We do not know of any reported recoveries. If patients are carefully selected for treatment on the basis of good general physical condition, and if medical and nursing care during treatment are adequate, fatalities from other causes than this may be almost completely avoided. The mortality from rupture of the spleen is certainly less than

0 1 per cent, not a great risk when one considers the potential gravity of neurosyphilis.

The urine should be examined every few days with especial reference to the presence of red cells. Albuminuria and cylindruria are of course common during the febrile period. Blackwater fever is extremely rare only one or two cases having been reported. Especial supervision of the urinary tract is essential in patients with cord bladders. In such instances, acute retention is common catheterization though often necessary should be carried out with rigid care to avoid or minimize infection. Ascending urinary infection is a grave complication of malaria therapy and in our experience has resulted fatally in 4 patients

MALARIA ROUTINE

Interrupt malaria temporarily or permanently for

1 Systolic B P below 70 mm. Hg. (cardiac collapse)
2. Persistent marked tachycardia in afebrile periods (pulse 120–140+)
3. Intractable nausea and vomiting.
4. Severe and deepening (not mild) jaundice.
5. Severe anemia (Hgb. 50%, R.B C. 2 0 million)
6. Rising N P N (above 60–80 mgms. %)

For temporary interruption of malaria, use
Bismuth thioglycollate (thiobismol) 0.2 gm. intramuscularly (one dose only)

FIG. 69

Volsky and Sheveleff have studied kidney function during malaria, but they lay little stress on nitrogen retention, which to some extent is almost universally observed The blood nonprotein nitrogen rises sometimes only slightly, sometimes to very high levels This phenomenon may at first be dependent on other causes than renal insufficiency but if it continues, kidney function may be seriously disturbed and uremia precipitated. To avoid this it is desirable to obtain blood nonprotein nitrogen estimations every 4–5 days particularly if the patient becomes increasingly drowsy and to terminate the malaria if the level exceeds 60–80 mgms. per 100 cc

Anorexia is a common feature of induced malaria. As a result of failure to eat, the patient may lose 10–25 pounds during the febrile period though this is quickly regained when the fever ends No special dietary precautions are necessary the patient may eat anything which tempts his palate. When solid food is repugnant, eggnogs made of half cream and half milk and containing an ounce of whisky will often provide adequate nourishment.

Karnosh and Williams have described an unusual and in their experi-

ence always fatal complication of malaria characterised by profuse hemorrhage from the lower bowel, due to non-inflammatory ulcers of the intestines. We have observed one such case which recovered.

The cerebral complications of natural malaria apparently occur in the induced variety with great rarity (Perwuschin) we have never seen an example. Transitory mental confusion or frank delirium at the height of fever is, however often noted (Masson)

Susceptibility of induced malaria to quinine—A striking difference between induced tertian malaria and the natural disease is the great susceptibility of the former to quinine. The average induced infection may be completely cured with as little as 1–8 gms. of any quinine salt. It is not definitely known on what this increased susceptibility depends, perhaps partly on the fact that the development of the parasite is largely asexual, partly because quinine is given relatively early, before the organism has become entrenched as in the natural disease, partly because the organisms may not have been previously exposed to quinine. At any rate, we have never seen a relapse in any patient with induced tertian malaria given adequate quinine therapy though relapse is said occasionally to occur when the disease is induced by the bite of a mosquito rather than by direct patient-to-patient transfer Our own experience in this respect is in accord with that of practically all other workers, and we cannot explain the curious report of Petersen who observed relapse in 14 of 261 patients. This phenomenon may be due to the employment of quinine-resistant strains. Should it occur atabrin and plasmochin should be administered in conjunction with quinine.

Quartan malaria is not so quinine sensitive, and relapse in patients treated only with quinine occurs in at least 10 per cent (Kroll) Treatment to terminate the quartan infection should be begun with atabrin (100 mgms.) and plasmochin (10 mgms.) each three times daily for 5 days this to be followed with the usual course of quinine for 10–14 days.

The termination of malaria—This extreme quinine sensitivity makes it possible to terminate induced tertian malaria at any desired point. Various preparations of quinine have been used. We employ either the sulphate or the dihydrochloride. The drug is given by mouth in

MALARIA ROUTINE

To end malaria permanently

A. Tertian—quinine sulphate 0.3 gm. (mouth) t.i.d. for 10–14 days.

B. Quartan—atabrine 100 mgms., and plasmochin 10 mgms., t.i.d. for 5 days, followed by quinine sulphate 0.3 gm. for 14 days.

Fig. 70

instances we have seen result in mild congestive heart failure At about the tenth day the patient may be allowed up for an hour increasing an hour daily graduated exercise may be cautiously resumed until full activity is reached within 2–3 weeks. Strength and appetite should be rapidly regained within a few days after the cessation of fever if the appetite is slow in returning, it may be stimulated by 10 units of insulin given twice daily 30 minutes before meals. If desired iron may be given for the anemia, though usually this is not necessary the blood returns to its pre-treatment level within 3 weeks. In most instances all the weight lost during the fever is regained during the first 2 weeks of convalescence and, indeed, the gain usually continues so that within a few months the patient is 10–30 pounds heavier than before treatment. Gain in weight is a favorable prognostic sign which can be definitely correlated with the probability of clinical improvement.

MALARIA ROUTINE

During convalescence

1. Complete bed rest for 7–14 days after last fever
2. About 4–5 days after last fever start intravenous neoarsphenamine 0.3–0.6 gm. Give 6 doses at 5–7 day intervals, largely for tonic effect.
3. If necessary use insulin 10 units twice daily 30 minutes before meals to stimulate appetite.
4. Resumption full physical activity gradual, over 3–4 week period.

FIG. 73

About 4–5 days after the completion of fever it is customary to start a short course (6 injections) of small doses (0.3–0.6 gm.) of neoarsphenamine or mapharsen (40–60 mgm.) given at 5–7 day intervals. This is done for its anti-malarial and general tonic effect, as well as for its possible antisyphilitic action in the event (see below) of the development of gummatous tertiary lesions outside the nervous system.

Immunity and reinfection in inoculation malaria Second attacks —In Gerstmann's monograph it is stated that the immunity produced by induced tertian malaria is neither complete nor long lasting, and that second inoculations are usually successful in producing a fresh infection, which is, however usually milder than the first. He has subsequently modified these views and in a personal communication in 1941 stated that reinoculation is usually successful only when it is practised within certain more or less definite time limits If it is carried out as soon as 3 months after or as late as 5 years after the original attack, it is usually completely successful. Later or earlier than this however it either fails completely or leads to an abortive malaria consisting of a few mild paroxysms only and ending spontaneously This is entirely in accord with

our own experience in some 60 patients in whom second attacks have been attempted. We have always been successful if the second attempt followed the first by as long as 5 years otherwise not unless it was within the first few weeks

This fact is important in two respects. If it is necessary for any reason to cut short a patient s malaria with quinine, reinoculation with the same strain may be practised with the certainty of a take within a period of 2–6 weeks, and the desired number of paroxysms completed However in the event of a clinical relapse of neurosyphilis some months or years after the termination of the first attack, reinoculation will be unavailing unless the interval has been 5 years or longer In such instances other methods of fever therapy may be used We agree with Nicole and Steel that second attacks of malaria sometimes produce clinical results lacking after the first.

Within the refractory period quartan malaria may be employed if desired. Immunity against the tertian organism does not extend to *P malariae*.

The mortality rate from malaria —The possibility of death as a result of induced malaria depends largely on two factors the proper selection of cases for treatment, and the experience and skill of physician and nurses. Kraus reporting on a large number of patients treated in this country with the tertian strain records 9 02 per cent of deaths in an unselected group of patients but only 1 02 per cent when careful selection weeded out poor risks Cole reports a mortality of 2.2 per cent among selected cases. Our own mortality (in 1 600 cases) is between 1 and 2 per cent. The figures given by Neymann (10–30 per cent mortality from malaria) are clearly due to his over-enthusiastic propaganda for electropyrexia, and are a gross overstatement. Almost the only unavoidable cause of death from malaria is rupture of the spleen the incidence of which does not exceed 0 1 per cent of cases treated.

Among 438 patients treated with quartan malaria (Fong, Kroll, and others) there have been 13 deaths a mortality rate of 2.9 per cent.

The time necessary for and the cost of treatment —The average patient wants to know what he is undertaking in point of time lost from work and probable cost. For tertian malaria it is necessary to count on at least 6 weeks away from work, of which 5 weeks must be spent in a hospital for the quartan variety about 8 and 6 weeks respectively It is inadvisable to attempt malaria therapy in the patient s home. The cost varies with the type of hospital accommodations chosen and the physician's fee it is concentrated within a relatively short period of time but if measured in terms of the total cost of all treatment necessary for neurosyphilis malaria is probably a saving both in shortening the total duration of treatment and the total expense

The histopathology of induced malaria —This important question has been studied particularly by the Vienna group of workers, and in this country by Bruetsch and Freeman. Their studies may be briefly summarized as follows —first, treponemes are usually absent from the brains of malaria-treated paretics, though they may be found in large

numbers in untreated patients (In one living patient Forster could demonstrate treponemes by darkfield examination of material secured by brain puncture before but not after malaria.) Next, the typical pathologic picture of paresis in the brain is altered by malaria either in the direction of normality or in the direction of the picture produced by meningovascular neurosyphilis. The inflammatory exudate in the meninges and about the blood vessels is rapidly organized exudate is resorbed and the architecture is reconstructed. Third there is evidence in various organs, including the brain, of marked stimulation of the reticulo-endothelial system especially of the histiocytes and of the undifferentiated mesenchymal cells. It is assumed that these phagocytic cells may in some way be able to destroy treponemes Fourth, the extent of improvement in the pathologic picture in the brain closely parallels clinical improvement or the lack of it. Indeed in some patients with long-standing remissions, the paresis seems from the pathologic standpoint to have been cured." Finally though evidences of anatomic improvement in the nervous system after malaria are common similar evidences of improvement in other organs are lacking Active lesions of syphilis may persist especially in cardiovascular apparatus and liver This last fact is a potent reason for the subsequent antisyphilitic treatment of malaria treated patients and a valuable argument for those who like ourselves, believe that the favorable effect of malaria in neurosyphilis is not wholly dependent on the element of fever

Alterations in the patient's immune status by malaria —Numerous observers notably Piles, have reported the later development in paretic patients treated with malaria of gummatous lesions of skin bone viscera or nervous system and both Solomon and ourselves have observed the appearance of interstitial keratitis after the fever treatment of juvenile paresis. Such lesions are excessively rare in patients with un treated parenchymatous neurosyphilis and conversely grave neurosyphilis is rare in untreated patients who develop late lesions of this type. They are generally interpreted as evidence of allergy It is suggested that malaria has in some way altered the patient s response to his own infection and by rendering him allergic more liable to lesions of a mesoblastic type but more resistant to the further development or progress of parenchymatous neurosyphilis.

The mechanism of action of malaria —There are numerous hypotheses to explain the favorable action of malaria. None are proved and many are entirely unacceptable. It will be obvious from what we have already said (p 372) that the destruction of treponemes by high temperatures is probably not the only factor Whether the stimulation of the reticulo-endothelial system, suggested by Bruetsch the theory of forced drainage of treponemes from the nervous parenchyma along the perivascular channels into the subarachnoid space, advanced by Freeman the direct action of malaria upon focal areas in the brain as proposed by Wagner-Jauregg alterations in the hemato-encephalic barrier advocated by Paulian and Tanasescu or still some other cause or combination of causes is operative cannot yet be stated.

Fever Produced by Non-Specific Protein Therapy

The method of producing fever by the intravenous injection of various types of vaccine was tried years ago by Wagner von Jauregg and abandoned in favor of malaria. Renewed use of the method was stimulated by the facts that in certain localities malaria was not available and that certain patients were immune to malaria. Reports of the efficacy of the method have been made in this country by Kolmer in experimental rabbit syphilis and in patients by Kunde, Hall, and Gerty (who provide an adequate bibliography) Kemp and Stokes, O'Leary and Brunsting and Kulchar and Anderson.

Kolmer found no evidence of pronounced curative activity in rabbit syphilis from intravenous injections of typhoid vaccine or Coley's fluid alone or in combination with chemotherapy Nevertheless all observers are agreed that in paresis particularly and in neurosyphilis generally the method has some value and a distinct field of usefulness. This conclusion is in accord with our experience which includes about 200 patients treated

The intravenous injection of a foreign bacterial protein is followed within 30–120 minutes by a sharp shaking chill, lasting 15–20 minutes during which there is a prompt rise in temperature to heights varying with the dose selected, but with suitable doses to 40 0–41 1°C. (104–106°F) The elevation of temperature is maintained at this height for about an hour gradually falling to normal within 8–10 hours. Associated with the chill is an elevation of blood pressure, which falls below normal as the chill ceases and the temperature rises. Such paroxysms of fever may be produced at any desired interval usually every day or every other day A course of treatment constitutes 12–24 paroxysms.

The substance used by practically all observers, including ourselves is the commercial typhoid-paratyphoid vaccine. As dispensed this contains 2,500 million killed organisms per cc. The initial dose must be small, to avoid serious danger to the patient the usual amount for the first injection, measured in terms of number of organisms, is 50 million. This is accurately measured by appropriate dilution of the stock vaccine with sterile normal salt solution, the total bulk of fluid injected being 1 cc All injections are given intravenously All patients develop a resistance to the protein and to secure temperatures of 39.3°C. (103°F) or over steadily increasing dosage is required. For the first few injections, the dose is usually doubled, i.e. 50 100 200 400 800 million organisms. Thereafter increments are added according to the patient's temperature response usually an increase of 400 million organisms per dose is sufficient. As the dosage increases the dilution of stock vaccine diminishes, so that finally as much as 2 or more cc of straight vaccine (5 000 million organisms) may be given.

Nelson suggests and we agree that the temperature is more effectively raised if the dose of vaccine is divided into two parts, the second injection being given at the peak of the fever induced by the first, i.e., 2–3 hours later We reproduce Nelson's table showing the results of this procedure in a specimen case (Table 84)

Absolute contra-indications to the use of the method are advanced

TABLE 84
INDUCED FEVER BY MEANS OF DIVIDED DOSES OF T.A B VACCINE
(AFTER NELSON)

Day	Dose of first injection, millions of organisms	Highest temperature	Dose of second injection, millions of organisms	Highest temperature
1	70	103 6	Preliminary treatment by single injections	
2	140	103 0		
4	25	99 0	25	104 6
5	35	100 6	35	104 6
6	50	98 6	90	105 2
7	90	99 0	140	104 8
8	200	99 0	380	106 0
9	400	100 0	500	104 0
11	100	98 5	150	101 0
12	550	99 9	500	106 0
13	750	100 0	750	106 2

Following a third dose of 200 million two hours later the temperature rose to 104.8.

cardiovascular disease and active pulmonary tuberculosis With care the mortality is very low Kemp and Stokes report one death as a result of treatment we have had no deaths. Treatment should be carried out in the hospital, never in ambulatory patients.

Indications for the use of bacterial protein shock in neurosyphilis are (1) in patients located far from medical centers so that supervised malaria or other types of fever therapy are not available (2) in patients refractory to inoculation with malaria (especially Negroes) or in whom a malarial infection has spontaneously aborted (3) to activate or reactivate malaria in patients with unduly long incubation periods or in whom spontaneous abortion of the malaria seems likely

The therapeutic results are decidedly less favorable than those obtainable with malaria. In paretic patients, remissions are fewer slower in developing and less prolonged. The method should be reserved for neurosyphilitic patients in whom malaria is not available

Induced Pyrexia with Relapsing Fever (*S. duttoni*) and Rat Bite Fever (*S morsus muris*)

Relapsing fever and rat-bite fever have been practically abandoned in the treatment of neurosyphilis

Fever Produced by Physical Means

Hot baths —The treatment of neurosyphilis by means of hot baths was first tried by Schamberg and Tseng later by Mehrtens and Pouppirt. By immersing the patient full length in a bath of a temperature of 43.3°C (110°F) the body temperature rises within an hour to 40.5–41 1 C (105–106°F) The temperature of the bath water is then gradually reduced until it corresponds with the patient s temperature. The patient is

left in the bath for an hour and on removal is wrapped in blankets which promotes slow defervescence A hot bath may be given daily, a series consists of 13–20 baths

The technique of this procedure is so complicated that its use must be confined to large institutions. A specially large tub is essential It must be provided with an automatic mixing valve to maintain the proper temperature of the water the patient's temperature is taken at 5 minute intervals by means of a rectal thermocouple and a trained attendant must be constantly available The method is not without danger cardiac collapse may occur Furthermore the reported results are inferior to those obtainable with malaria. We have had no experience with the method.

Mechanically Induced Fever

During the past ten years numerous electrical devices for the production of artificial fever have been introduced for the hyperpyrexial treatment of syphilis and other diseases. They were evolved on the assumption that hyperpyrexia *per se* is responsible for the benefits of fever therapy and because it was felt that they would permit more accurate control of the temperature response, thereby rendering treatment less dangerous Each method has its firm adherents who believe not only that it is superior to other physical agents for the production of fever but that electropyrexia of any type has certain advantages over malaria. Although neither of these contentions is proved there is no doubt of the beneficial action of mechanical fever in the treatment of neurosyphilis. The question of the best and safest means of producing it remains unsettled. In the meanwhile the method of choice should be (a) that most readily available and (b) that with which the physician is most familiar None of the machines devised so far is foolproof and no matter how perfect they are mechanically the efficiency and safety of their performance is directly proportional to the skill and experience of the operator They must be employed in a hospital, never in the physician's office. The constant attendance of an experienced nurse or technician and of a supervising physician is necessary not only during the time the patient is receiving treatment but for several hours thereafter Unless these requirements can be fulfilled and in addition unless there are readily available every possible means to deal with the accidents consequent to treatment, fever therapy by mechanical means should never be attempted. These considerations are particularly important in view of the increased tendency to consider it a safe office procedure. The dangers of electropyrexia are practically the same for all types of apparatus They are listed by Neymann as follows

1 The main dangers of artificial fever produced by physical means are exhaustion burns and death.

"2. Death as the result of electropyrexia is a rare occurrence and can be avoided by good clinical judgment and proper care.

"3 Heat stroke can and must be avoided. Patients must never be allowed to reach a temperature above 42.5°C. (108.5°F) Under ordinary conditions a maximum temperature of 41.5°C. (106.7°F) suffices for all

clinical needs Pyrometers are valuable for recording a patient s temperature from moment to moment.

4 External heating is more exhausting than penetrating heat. It reverses the natural thermal gradients of the body by heating the skin higher than the viscera. It also deprives the body of its physiological safety valves by heating the extremities to the same degree as the torso It relatively increases the heart rate and decreases the sweat production.

5 Adding moisture to the air of a hot air cabinet makes the heating of the patient more efficient but does not alter the unphysiological action of external heat. The much lauded and socalled intrinsic value of air-conditioning alone is therefore a myth

"6. Burns can be avoided by proper technic. Conventional spark gap diathermy machines are inclined to cause a liquefaction of the subcutaneous fat and should not be used for producing fever in very obese individuals *No machines are fool proof All may cause burns if improperly* used. This applies to electric blankets diathermy machines radiotherms hot air cabinets with or without air-conditioning and inductotherms

"7 It is important to attempt to replace the sodium chloride lost through perspiration by having the patient drink six tenths per cent sodium chloride solution during treatment. The tendency towards acidosis may be influenced by giving fruit juices and sugar solutions.

An increasing number of physicians feel that a little fever therapy is better than none at all and therefore recommend weekly or bimonthly treatment to patients who cannot arrange for it at closer intervals One of us (Kemp) has observed 50 cases of neurosyphilis treated with weekly hyperpyrexia. Although the results were better than those following routine chemotherapy alone they were decidedly inferior to those following fever given more frequently even though the total number of treatments was the same. In view of the dangers the results of this manner of giving fever treatment do not seem to justify the risk.

Diathermy

Neymann is a firm believer that the only beneficial feature of the various methods of fever therapy of neurosyphilis is the fever He therefore evolved the idea of elevating body temperature by means of diathermy The following description is largely drawn from his papers (Fig. 74)

The diathermy machine is capable of delivering under load not less than 7500 ma and 35–100 v and has a frequency of 500–1500 kilocycles. The electrodes, one each for the patient s back and front, measure about 16×18 inches they are fenestrated and the edges scalloped to reduce the possibility of burns. They are made of pliable metal about 0.3 cm. thick, and are backed by a removable sheet of sponge rubber about 1 cm. thick. The patient s trunk is anointed with a conductive jelly the electrodes applied front and back, and held in place by a laced canvas jacket. The patient is placed in bed surrounded by numerous blankets. The current is gradually turned on to about 3000 ma., which is followed in 15–30 minutes by profuse sweating. This lowers skin resistance and the current may be gradually increased usually not above 4000 ma. Temperatures are recorded at least as often as every 15 minutes by means of a rectal thermocouple. The rapidity extant and duration of temperature rise may be

controlled at will. During the period of fever there is moderate dehydration increase in pulse, and respiration, a rise of systolic and a fall of diastolic blood pressure, and transient changes in blood chemistry (increase in NPN) Treatments may be given every 2 days or twice a week, and may be continued more or less indefinitely Neymann has given as many as 49 treatments to a single patient.

Objections to the method are —(1) the apparatus is expensive available only in large hospital centers and necessitates trained medical and nursing attendants (2) with slight slips in technique, serious burns may occur (3) deaths from uncontrollable hyperpyrexia have occurred (4) while the results obtained by Neymann and his associates seem to be as

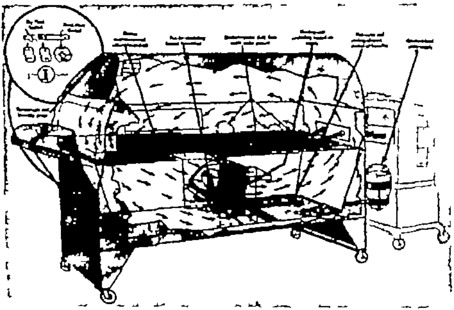


FIG. 74.—The Burdick Fever (Diathermy) Cabinet.

good as those obtainable with malaria, later investigators (Cullins Morgan and Seymour Epstein, Solomon and Kopp) feel that although diathermy is superior to other mechanical methods for producing fever the ultimate results are less satisfactory than from malaria. In any case, patients have been followed for too short a time to permit a final evaluation of the method.

The use of diathermy should at least for the present, be limited to the treatment of paretic patients in large medical centers. It is still in the experimental stage and is not advised for general use.

Short-Wave Radio

Various experiments on animals dating from 1924 (reviewed by Neymann) had shown that the body temperature of small mammals could

be elevated by placing the animals within the field of short wave radio transmission (waves oscillating between 6–80 000,000 per second) It was accidentally noted that the same phenomenon is true of human beings. An apparatus has been devised by the investigators of the General Electric Company to take advantage of this fact. A brief description is quoted from Carpenter and Page.

> The equipment used has been constructed on the same principle as a short wave radio transmitter with the exception that the energy is concentrated between the two condenser plates instead of being directed from an aerial. The heating consists of a vacuum tube oscillator This high frequency oscillator is composed of two 500 watt radiotrons operating at a frequency of from 10 000 to 14 000 kilocycles, the output of which is concentrated between the plates. The rectifier is an oil immersed transformer having a 7000 volt secondary and feeding two half wave hot cathode, mercury vapor tubes. In conjunction with a filter system, this unit furnishes the 3000 volt D C plate supply for the oscillator An auto-transformer is connected on the primary circuit of the high voltage transformer to provide plate voltage regulation. The condenser plates are aluminum, 28 inches by 18 inches by ⅛ inch and are covered with hard rubber plates 30 inches by 20 inches by ¼ inch to prevent arcing should the patient or attendant come in contact with the plates. In this field of undamped waves between the plates, there is a rapid alternation of 3000 volts drop of potential The greatest heating has been obtained by the use of a 30-meter wave that oscillated 10 000 000 times per second between the plates. This is the same type of short waves that is used in broadcasting long distances.

The patient is placed between the plates and is wrapped in blankets or is kept warm and dry by a process of air-conditioning with a continuous flow of hot air The temperature rises to 40 0–41 1 C (104–106°F) in about an hour Objections to the method are (1) the apparatus is expensive and obtainable only in large medical centers (2) burns may occur especially in disturbed patients (3) results have been reported in only a few patients, these followed for only short periods of time.

The method is not extensively used in this country

The Blanket Method

The following description of the blanket method for producing hyper pyrexia is taken from Epstein.

> Upon admission to the hospital the patient nude, is placed upon a bed which is covered with a thin bath blanket, a rubber sheet, a canvas sheet and two heavy woolen blankets. These are large enough to be completely wrapped around the patient. The heels are covered with a gauze pad and long heavy woolen socks are drawn over the feet and legs The patient is then wrapped with thin bath blankets in such a way that no portion of the body is exposed except the face. The limbs and trunk are covered separately and one blanket is brought over the head as a hood. This procedure requires five blankets.
>
> A common electric body frame large enough to cover two-thirds of a hospital bed and containing twelve 60-watt carbon lamps is then placed over the patient. This is used to accelerate the initial rise in temperature The frame should be made of light material and the patient protected from the lamps by a coarse wire netting.

The heavy woolen blankets under the patient are brought over the appliance forming a closed cabinet. The lights are turned on, and the patient s temperature rises promptly—that is, within two hours—to 40°C (104 F) The apparatus is then removed, and the patient is wrapped successively in the rubber sheet, the canvas sheet and the two heavy woolen blankets. This should be done in such a manner that he is completely enclosed in the pack. However the wrappings should be loose enough to permit some freedom of movement. Temperature is taken orally or by axilla.

Following the removal of the apparatus the patient remains in the blanket pack for the duration of the treatment. The usual treatment is five hours with a *temperature of over 39.5°C (103 1°F) but this will vary with each condition.* As a rule the entire treatment requires seven hours. While the patient is in the blanket-pack, the temperature tends to rise gradually When it reaches the desired height, it can be maintained at that level easily by loosening the blankets for a time.

The session is discontinued by removing the blanket-pack, changing the bedclothes and bathing the patient. The temperature falls to normal usually within one hour and a half

Although this method has the advantage of being extremely simple and has been further simplified by Kelly it is not generally used. It is consequently impossible to determine its comparative value among the other fever-producing agents.

Fever Cabinets

The radiant light fever chamber introduced by Carpenter and Warren is the simplest of all the fever cabinets It consists of a light frame in which the patient surrounded by electric bulbs is placed for the duration of the treatment. More recently several types of air-conditioned fever chambers

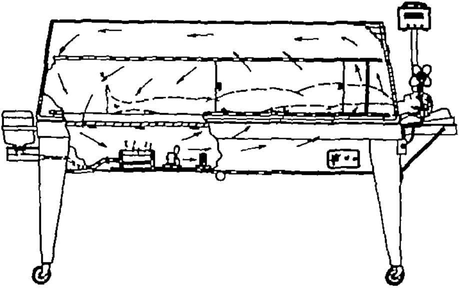


FIG. 75.—The Kettering Hypertherm (Courtesy of Dr Walter Simpson)

have been introduced The prototype of all of them is the Kettering hypertherm the following description of which is taken from Desjardins Stuhler and Popp

This chamber consists of a rectangular box about 6 feet long, 30 inches high and 36 inches wide mounted horizontally on long legs and divided into two unequal parts one the main compartment occupied by the patient, is large enough to accommodate the trunk and extremities the other is a small shallow compartment at the foot of the chamber and separated from the main compartment by an asbestos partition in which is a small open grill in this smaller compartment is mounted the simple mechanism designed to heat and humidify the air as well as to force it to circulate through the chamber proper The ceiling of the chamber is double and the anterior third of the inner layer of the ceiling contains a large number of holes, through which the heated and humidified air furnished by the generating mechanism penetrates the main compartment of the chamber and circulates around the patient. The floor of the chamber also is double, and its inner layer constitutes a bed which, moving smoothly on brass rollers, can be rolled into the chamber or withdrawn from it with little effort. The bed is covered with a comfortable air mattress. The two legs supporting the head end of the chamber are double and one set, forming an integral part of the rolling bed is fitted with casters to facilitate the inward or outward movement of the bed.

At the head end of this bed is a projecting shelf which remains outside the chamber when it is closed and on which rests the head of the patient This end of the chamber can be closed by means of a vertical panel which sliding in metal grooves at each side can readily be lowered or raised once closed, this panel is firmly held in place by two large hand screws. One turn of these screws permits the panel to be quickly raised, and the patient can thus be withdrawn from the chamber in five seconds. In the center of the lower border of the vertical panel is a rather large and deep circular indentation that surrounds the patient s neck. Within this main indentation is fixed a piece of sponge rubber in which a smaller secondary indentation fits loosely around the neck. In order to provide for variations in the size of the neck of different patients, and to prevent the escape of air which would reduce the efficiency of the apparatus and interfere with treatment, the space between the rubber and the neck is loosely packed with a towel.

The side walls and ceiling of the chamber are made of heavy celotex, while the floor is made of wood. It is essential that the chamber should be as air tight as possible.

The thermogenic mechanism consists of a small electric air heater with three units this is controlled by external switches which make it possible to use one or all three units at will and also by a thermostat which permits one to regulate the temperature of the air within the chamber and a pan of water heated by two small electric elements, *the heating of the water for humidification being* regulated by an automatic humidistat. But in order to avoid uncertainty about the degree of humidity this factor is verified by dry and wet thermometric readings The data thus obtained permit the exact calculation of the degree of humidity The heated and humidified air thus produced is then forced by an electric blower between the two layers of the ceiling of the chamber whence it enters the main compartment through the holes in the anterior portion of the inner layer of the ceiling, circulates around the patient about ten times a minute and returns to the heating and humidifying mechanism through the grill in the partition that separates the patient from the mechanism.

By means of panels sliding in metal grooves at each side it is possible to keep the patient's skin under observation, to take the blood pressure as often as may be necessary and to take the rectal temperature every few minutes. Moreover in case of emergency the patient may be withdrawn from the chamber in a few seconds. These undoubtedly are advantages which are not provided for to the same degree by any other method or apparatus with which we are acquainted.

The relative value of the cabinet method of producing hyperpyrexia has not been determined As with the other mechanical fever devices it has its firm adherents and as with all types of fever therapy it is necessary to have the patient under the constant observation of a trained attendant and a supervising physician

The Simultaneous Use of Fever and Chemotherapy

On the assumption that the penetrability of the central nervous system to arsenicals might be increased during fever several groups of observers have studied the effect of simultaneously administered fever and chemotherapy in experimental animals and neurosyphilitic patients. From the clinical standpoint Kemp and Stokes, who first reported this procedure, thought that the results were better in patients so treated than in those in whom the course of fever was followed or preceded by courses of tryparsamide or arsphenamine. More recently Hinsie and Blalock arrived at opposite conclusions Bennett and Lewis treated 72 patients all but ten of whom had obvious and in many instances advanced neurosyphilis simultaneously with fever and bismarsen or mapharsen. The results according to these observers, were brilliant in many instances. The data as to clinical results, while meagre, are suggestive that this procedure may have some value and this assumption is further strengthened (though not proved) by the studies of Paulian and Tanasescu, who have shown that the concentration of arsenical in the spinal fluid is much greater when neoarsphenamine is given simultaneously with malaria than when it is given alone.

Tryparsamide

Considerations leading to the use of tryparsamide in neurosyphilis Its mechanism of action—The use of tryparsamide (see Chapter VI) in neurosyphilis was orginally begun on the basis of considerations of its action on the animal organism, of its effect on experimental trypanosome and treponeme infections and of the biology of syphilitic infection. The drug has a high arsenic content (25 per cent) and is relatively non-toxic for animals After the administration of toxic but sublethal doses, symptoms of intoxication develop promptly but as rapidly clear There is no evidence of cumulative toxic effect Both in animals and in man normal and diseased there is a remarkable stimulative effect evidenced chiefly by a prompt gain in weight and improvement in general appearance and activity Furthermore, toxic doses of the drug cause in animals peculiar nervous symptoms, indicating its penetration into the nervous system.

While its trypanocidal effect in mice or rats (in which animals trypanosomiasis is predominantly a blood stream infection) is relatively low

as compared with that of other arsenicals it is highly effective in experimental trypanosomiasis of rabbits (predominantly a tissue infection) This indicates that tryparsamide possesses a high therapeutic tissue penetrability The treponemicidal action of the drug is distinctly less than its trypanocidal action and its therapeutic ratio in rabbit syphilis is between 1 1 and 1 2 as compared with the arsphenamine ratio of 1 10 It was found, however (Brown and Pearce) that the favorable influence exerted by the drug in rabbit syphilis is out of proportion to its immediate spirocheticidal effect. It appears to augment and hasten spontaneous recovery

As Brown and Pearce put it in syphilis

Little or nothing could be expected from the standpoint of spirocheticidal action—at least in those stages of the disease in which spirochetes are numerous in all parts of the body or at a time when no resistance has been developed to oppose the progress of the infection, unless very large doses of the drug could be used. It is hardly necessary to say that, under conditions such as these the surest means of effecting an immediate control of the infection is the use of some powerful spirocheticidal agent

During later stages of the infection, when spirochetes have become localized in parts of the body that are therapeutically inaccessible to the ordinary spirocheticidal agent or when the factor of resistance comes into play and the course of the disease is determined largely by the resistance that the individual can bring to bear therapy becomes a distinctly different problem Here one may with reason use measures that under other circumstances would be inapplicable. Treatment becomes a question of reaching inaccessible foci of infection, and this might be done either by the use of suitable spirocheticidal agents or by the use of agents whose primary function is to reinforce the resistance of the patient or better still by the use of substances that combine both of these qualities of action.

According to our conception of the biology of syphilitic infections, involvement of the central nervous system is primarily a matter of defective or ineffectual resistance—a conception that is applicable irrespective of any decision that may be reached as to the character of the spirochete concerned in these infections. Moreover it appears that the conditions for the growth of spirochetes in the tissues of the central nervous system are not so good as in many other parts of the body and hence their resistance to noxious influences should be correspondingly less

As may be seen, these conditions are such as would enable a drug with a moderate or even low spirocheticidal action to produce a maximum effect in the central nervous system provided it possessed a high degree of penetrability What is more important, however is the opportunity afforded for inducing an involution of the infection by reinforcing natural processes of resistance as has been done by the use of various methods of nonspecific stimulation. Obviously this applies to infections involving the nervous tissue of the brain and cord more than it does to those of other parts of the nervous system which occupy a different position in the general scheme of evolution of syphilitic infection

Clinical and serologic effects of tryparsamide —Lorenz and his associates were the first to use this drug in the treatment of neurosyphilis followed shortly by ourselves and later by many others The predictions made from the experimental studies were almost entirely borne out in

practice. The first striking effect of the drug is usually a gain in weight and improvement in the general physical status of the patient. In paresis, remissions occur in about 30 per cent of the patients treated and in tabes and diffuse meningovascular neurosyphilis, symptomatic improvement is often prompt and satisfying.

Except in neurosyphilis, however the drug is without apparent benefit, and should not be used. The risk of damage to the optic nerve is too great to justify its use unless the possible therapeutic benefit is commensurate with the risk. This one fact limits the field of usefulness entirely to neurosyphilis. Even here however it should not be employed as initial treatment in patients in whom maximum treponemicidal effect is desired e.g in early meningeal neurosyphilis.

The serologic results from tryparsamide are much less striking than clinical results. There is little or no effect on the serologic tests of the blood. Excess cells and protein in the spinal fluid usually disappear promptly Wassermann and colloidal curves are reduced to negative in a fair proportion of patients with meningovascular neurosyphilis but much less frequently in tabes and paresis.

Methods of use of tryparsamide —At the outset and while the use of this drug was in the experimental stage, it was used alone or in combination with a heavy metal. More recently since its place in the therapy of neurosyphilis is more firmly established, we have employed it as one feature of a more complicated therapeutic attack in which fever other arsenical drugs, and the heavy metals all figure In paresis it is ideal follow-up treatment after fever therapy which should always be employed first when possible. In other forms of neurosyphilis it is our custom to try the clinical and serologic effect of six months' treatment with the arsphenamines and heavy metals before resorting to tryparsamide. If improvement from the preliminary period is not definite, tryparsamide is used at some time in almost all patients.

The average (and maximum) therapeutic dose is 3 gms intravenously We agree that there may be some advantage, so far as the incidence of visual reactions is concerned in starting with a smaller dose (the first of 1 0 gm. the second of 2.0 gms., the third and succeeding doses of 3 0 gms. each) A minimum course consists of 12 weekly injections but the administration of the drug may be prolonged indefinitely Stokes, Solomon, and ourselves having given as many as 100 consecutive weekly injections.

Prolonged use of the drug (50 or more injections as a minimum) is productive of much better results than a short trial. Solomon believes and we agree, that clinical improvement, if it occurs at all, is fairly prompt (3–4 months) but that to obtain lasting serologic improvement in the spinal fluid years of treatment may be necessary

Contra indications to and reactions produced by tryparsamide —There are no contra-indications to the use of this drug except partial optic atrophy Even patients with cardiovascular syphilis tolerate it without the difficulty caused by the arsphenamines and it can frequently be given to a patient who is sensitized against arsphenamine. The only reaction seriously to be feared amblyopia, is discussed in Chapter VII.

Every physician who uses this drug should be familiar with this reaction and with the essential precaution of preliminary ophthalmologic examination to prevent serious disaster

In recent years however reactions formerly rarely if ever observed with tryparsamide are beginning for some unknown reason to appear Our experience in this respect coincides with that of Kopp and Solomon who report a sharply increased incidence of reactions since 1937 Among these are nitritoid and gastro-intestinal reactions dermatitis (both fixed and generalized) jaundice, and various vague cerebral phenomena (cf pages 124–125)

Most of the recent literature on tryparsamide is ably and succinctly reviewed by Hinrichsen.

Subdural Treatment

The lack of improvement of many neurosyphilitic patients (especially tabetics and paretics) after the intravenous administration of the arsphenamines and the recognition of the existence of the hemato-encephalic barrier (p 370) led to attempts to introduce medicaments into more direct contact with the diseased tissues. It was thought that this could be accomplished by intraspinal injection Marinescu abroad and Swift and Ellis in this country were the first to employ the use of homologous arsphenaminized serum. This was modified promptly by Ravaut and by Gennerich who utilized neoarsphenamine in doses of 1–6 mgms. dissolved in normal saline or in spinal fluid and by Ogilvie who reinforced arsphenaminized serum by the addition of arsphenamine in minute quantities Later still the use of mercurialized serum was attempted but promptly abandoned. Further efforts to modify the method were made by varying the route of administration i.e intraspinal intracisternal intraventricular

The intervening years have witnessed the usual phenomena attending the introduction of a new method of treatment—its application to all types of neurosyphilis its success in some its failures in many Its dangers have become obvious Its method of action has been furiously debated with its proponents and opponents sometimes becoming seriously over heated. Without going into the details it is necessary only to say that in most large syphilis clinics including our own a middle ground has finally been arrived at. Subdural treatment is still used in certain selected cases (usually in tabes dorsalis) and for particular indications. The medicament used is usually arsphenaminized serum without reinforcement, this procedure having been abandoned as too dangerous The route of administration is intraspinal or intracisternal intraventricular treatments have been abandoned

The mechanism of action of subdural treatment —There are three theories as to the manner in which subdural treatment may effect improvement in neurosyphilis First the substance introduced may be treponemicidal. This seems highly improbable since the quantity of an arsphenamine injected i almost infinitesimally minute whether given direct or as arsphenaminized serum and since the material injected is

probably promptly absorbed from the cerebrospinal system by the blood stream. Second the injection sets up an aseptic meningitis demonstrable by symptoms and by spinal fluid cell counts at intervals after treatment. The meningeal reaction persists for 24–48 hours. It is thought that the hyperemia which it induces may be beneficial. Third, the induced meningitis may alter the permeability of the hemato-encephalic barrier so as to permit the entrance into the nervous system of substances—drugs or protective bodies—otherwise barred out.

Which of these explanations is the correct one is not known probably one of the latter two since good clinical results have been obtained from the subdural injection of such non-specific substances as normal human serum or air At any rate the problem is one for the investigator rather than for the practitioner

The field of usefulness of subdural treatment —The experience of many years has shown that subdural treatment is of little or no value in paresis. For two particular manifestations of tabes it accomplishes results sometimes securable by no other form of treatment, i.e. primary optic atrophy and intractable lancinating pains (Chapters XX and XXIV) In other forms of neurosyphilis it is of value if at all only in the sense of shortening the duration of treatment. The ultimate outcome is no better when it is used than when it is not. The method is distinctly contra indicated in tabetic patients with marked sphincter disturbances which are likely to be made suddenly worse, and in those rare patients with an already existing paraplegia due to endarteritis of vessels in the cord.

The choice of subdural medicaments —Speaking entirely from our own experience, the substance of choice for subdural treatment is arsphenaminized serum prepared with slight modifications from the original technique of Swift and Ellis. Reinforcement of the serum with arsphenamine (after Ogilvie) is productive of a greater number of serious reactions and the direct use of arsphenamine or neoarsphenamine dissolved in spinal fluid far too dangerous Mercurialized serum has been abandoned largely because of reactions which were more productive of discomfort than of danger We have no personal experience with the injection of air

The technique of preparation and administration of arsphenaminized serum —The method which we employ is that elaborated by Fordyce.

The patient is given an intravenous injection of 0 6–0 75 gm. neoarsphenamine or 0.3 to 0 4 gm. of arsphenamine. From 10–30 minutes after injection, 30–60 cc of blood are removed into a sterile centrifuge tube which is allowed to stand overnight in the icebox for separation of the clot. This amount of blood withdrawn at this interval contains less than 0 5 mgm. of drug. The next day, under sterile precautions, the tube is centrifuged, the supernatant serum poured into a fresh sterile tube, recentrifuged to remove all blood cells, and transferred to a third

If there is a contra-indication to the intravenous injection of this dose of neoarsphenamine, e.g., cardiovascular syphilis, the drug may be given to another patient, his blood withdrawn, and the heterologous serum administered to the neurosyphilitic patient. If this procedure is adopted, the patient chosen as a donor should have late rather than early syphilis, to avoid the possibility of inoculating the recipient with additional treponemes.

tube The serum is then inactivated for 45 minutes at 56°C The inactivation not only destroys complement, but also kills any bacteria which may have been introduced (except spore bearers) The serum is now ready for administration.

A lumbar (or cisterna) puncture is performed with the patient in the lateral recumbent position in bed. As soon as the dura is perforated, a sterile graduated cylinder fitted with an adapter and 10–12 inches of rubber tubing, including a glass window is attached to the puncture needle, and 10–15 cc. of spinal fluid syphoned off by means of holding the cylinder well below the level of the puncture wound. (Unless the flow of fluid is free, the procedure must be interrupted and another puncture made. If puncture results in a bloody tap, treatment should be postponed for a week.) This amount of fluid is decanted into three sterile tubes for testing. While the cylinder is held at the level of the needle, the desired dose of serum, warmed to body temperature, is poured into it, first flaming the edge of the tube in which the serum is contained. The cylinder is then lowered again below the level of the needle, so as to syphon off additional spinal fluid. Since spinal fluid is of lighter specific gravity than blood serum it rises to the top of the cylinder When the cylinder contains a total volume (serum and spinal fluid) of 25–30 cc it is gradually raised above the level of the needle and the mixture allowed slowly to flow back in by gravity When the cylinder is empty the needle is rapidly withdrawn. During the syphoning off *of spinal fluid the patient will usually complain of severe headache when 25–30* cc. has been withdrawn. This will be promptly relieved as soon as the mixture flows back in. The mixing of serum and fluid is calculated first to reduce somewhat the irritating properties of the serum, and second, by virtue of the fact that spinal fluid rises above the serum in the cylinder to push the serum to a higher level in the dural canal than the lumbar sac, where it might otherwise remain.

As soon as the injection is completed and a sterile dressing placed over the puncture wound the patient is instructed to lie on his face, in order to minimize leakage through the puncture wound in the dura. He is to maintain this position as long as he is comfortable and at least for 2–3 hours. The foot of the bed is elevated 12 inches for a period of 4–12 hours, to promote the flow of the heavier serum away from the lumbar sac cerebralwards (Vrančić, Sachs, Wilkins, and Sams) Liquid diet is ordered for 24 hours and, for the relief of discomfort, morphia 10 mgms. is given as a routine two hours after treatment and thereafter as necessary not oftener than every 4 hours.

Subdural treatment should always be given in a hospital, rather than in office or patient s home and a minimum hospital stay of 24–48 hours should be demanded The physician inexperienced in the method should never attempt it his patients in whom it is indicated should be referred to the expert.

Dosage intervals between treatment and routes of administration —The dose of serum to be administered subdurally should never exceed 12 cc and at the start of a series of treatments 5 cc. is a safer dose. Larger amounts may cause serious damage. The interval between treatments should be a full two weeks and no more than 6 treatments should be given in a series The route of administration will vary with the condition for which treatment is indicated intracisternal for optic atrophy or for lancinating pains in thorax and arms, intraspinal for ataxia or pains in the legs The question of intracisternal treatment in optic atrophy is more fully discussed in Chapter XX

The dangers of subdural treatment —Reactions are much more

frequent after intraspinal than after intracisternal treatment. If the patient complains of violent pain in the rectum perineum, genitalia, or legs actually during injection the procedure should be interrupted at once it is probable that the serum is infiltrating a fibre of the cauda equina. Usually there is no discomfort during injection nor for 2–3 hours thereafter Then, however the patient begins to suffer with pains in the legs, which are typically lancinating in character These are much worse if the patient has been subject to lightning pains before treatment, and in any case, usually require to be controlled with morphia. There may be severe headache mild stiffness of the neck and slight elevation of temperature. Nausea and vomiting sometimes occur lasting for 18–24 hours. In the average patient, all these symptoms subside within a day

The danger of subdural (especially intraspinal) treatment however lies in the production of irritation of the lower cord sometimes ending in transverse myelitis and complete paraplegia. Such an accident is usually initiated by numbness of the perineum and genitalia (saddle anesthesia) and bladder paralysis. In some patients this clears up rapidly in others persists as such for weeks and months, and in a few is followed by complete paralysis of the lower extremities and loss of sphincter control. When this occurs the condition is usually permanent, the patient is a hopeless bedridden invalid dying of ascending urinary infection. We have seen this accident in six patients, four of whom were treated elsewhere. It is much more likely to occur after the direct subdural administration of the arsphenamines or after reinforced arsphenaminized serum than when the Swift-Ellis technique is used. Too large dosage too short an interval between treatments and too many treatments in a series, are contributory factors. We have seen no reports of myelitis after intracisternal treatment.

The treatment of neurosyphilis by spinal drainage —The popularization of spinal drainage (i.e. removal of all the fluid securable by lumbar puncture just before or after an intravenous injection of an arsphenamine or tryparsamide) is an offshoot of the now defunct argument as to the value of subdural therapy Certain of the opponents notably Dercum, of this latter method of treatment produced elaborate arguments, physiologic and otherwise to show that subdural treatment was unsound in principle and wrong in practice and suggested that its entire benefit was due to the associated removal of spinal fluid. As with many other procedures in medicine the proof of the value of spinal drainage lay not so much in polemic argument as in actual results obtained in patients. Among others Stokes and Osborne reported that routine treatment plus spinal drainage was no more effective than routine treatment alone and in this opinion we entirely concur Repeated spinal drainage in a neurosyphilitic patient will reduce the cell count toward normal otherwise it has no effect, and is a thoroughly discredited and abandoned method of treatment.

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Chapter XXIV

THE TREATMENT OF NEUROSYPHILIS THE APPLICATION OF TREATMENT METHODS AND RESULTS

The complexity of the problem of the treatment of neurosyphilis makes it difficult to write in general terms and yet, because of the very diversity of conditions confronting the therapist it is impossible to offer too specific suggestions as to the individual case. In each patient the physician must evaluate for himself such factors as the association of other lesions of syphilis especially in the cardiovascular apparatus and of other complicating diseases as age of the patient as the extent of actual or potential incapacity as the social problem involved as the type of neurosyphilis and the probable relative extent of inflammatory and degenerative changes it has produced as the ultimate prognosis as economic status in relation to the cost of treatment or to reduced or cancelled earning capacity as the desirability of various methods of treatment in relation to all these factors. The successful therapist is he who best envisages his patient's problem as a whole. The following discussion of treatment is written from the point of view of application to a group of patients in whom the possible complicating elements have been purposely blurred in order to provide a background of information as to the results obtainable in the average. It is recognized that in the individual patient, particular circumstances may lead to a complete revision of treatment plan and may seriously modify the expected result. In such situations the practitioner will find that consultation with an expert syphilologist often clarifies his problems and improves the outlook for his patient, while retaining the active management of the case in his own hands.

Classification of treatment systems in relation to types of neurosyphilis —As we have already pointed out, it is of the utmost importance both to patient and physician that the type of neurosyphilis be correctly classified before treatment is begun. Detailed physical, neurologic and psychiatric examinations and serologic studies of blood and spinal fluid are necessary Armed with this knowledge the physician is enabled to select treatment methods appropriate for the particular situation.

It is rarely possible to plan an outline of treatment for neurosyphilis for more than six months in advance Not only may unforeseen contingencies arise but also this length of time is usually necessary to observe the effect, both symptomatic and serologic of the plan of attack chosen. Symptomatic relief and a tendency toward serologic reversal may indicate that since the desired result is being achieved the original plan may be continued failure to secure improvement of one or both types often indicates the necessity for a shift in drugs the intensification of treatment or the introduction into the treatment scheme of a new method. More than in

any other type of syphilis treatment must proceed by a system of trial and error As a general rule it is wisest, unless special indications are present to reserve those methods of treatment—tryparsamide, subdural treatment, or fever therapy—which involve a risk to vital functions or even to life, until trial has demonstrated the inefficacy of the less danger ous trivalent arsenicals and heavy metals. Where exceptions to this rule exist in certain types of neurosyphilis they will be indicated in the appropriate paragraphs

There are, again speaking generally six systems of treatment available for neurosyphilis The results obtained by each of these systems in various types of neurosyphilis have been studied in the Johns Hopkins material by Hopkins and Moore and our remarks as to their appropriateness under special circumstances are based largely on their experience. These systems may be briefly summarized as follows

1 Routine antisyphilitic treatment similar to that used for late syphilis in general, i.e. courses of an arsenical drug alternating with courses of a heavy metal preferably bismuth, together with large doses of potassium iodide by mouth. The representative arsenical course consists of 6–12 *injections at weekly intervals in moderate dosage (0.3–0 4 gm. arsphenam* ine or 0.3 gm silver arsphenamine 0 6–0 9 gm. neoarsphenamine 0 06 gm. mapharsen) A representative heavy metal course consists of 8–12 weekly intramuscular injections of an insoluble bismuth salt. So far as possible treatment is continuous though if the infection is of more than 4 years duration an occasional rest period is permissible

We employ this plan only when the evidences of neurosyphilis are minimal, i.e. in early or late asymptomatic neurosyphilis with minor fluid changes (pleocytosis and protein increase only) or in late syphilis when the patient presents minor neurologic signs together with normal spinal fluid findings. With some modifications to be specially mentioned later this plan is also suitable for patients with vascular neurosyphilis, in whom there is no evidence of a complicating aortitis.

2 Mild routine treatment, in which the arsenical preparation usually neoarsphenamine or mapharsen is given in longer courses of 10–20 injections and in smaller dosage (0.3–0 45 gm. neoarsphenamine 0 03–0 04 gm mapharsen) with relatively more heavy metal.

This plan is particularly applicable to vascular neurosyphilis with com plicating aortitis to certain tabetics (excepting those with gastric crises or early progressive optic atrophy) and as tonic treatment to elderly patients or those in poor general physical condition. Even this relatively mild treatment will often be productive of marked symptomatic though little serologic improvement.

3 Intensified routine treatment in the direction of relatively more arsphenamine and less heavy metal. More arsphenamine means larger doses longer courses and a shorter interval between doses. A representative course consists of 12–16 injections of arsphenamine (0 4–0 6 gm.) or silver arsphenamine (0.3 gm.) neoarsphenamine is less suitable for this plan. (The rôle of mapharsen in a treatment scheme of this type has yet to be determined) The interval between injections may be 4 or 5 days in-

stead of a week. Treatment is usually continuous and when the plan is applied to early neurosyphilis must be so

This plan of treatment is adequate for most patients with early meningeal neurosyphilis (including neurorecurrence) with whom it is the method of choice. Rarely is it necessary to resort to more drastic measures It is also applicable to patients with early or late asymptomatic neurosyphilis (excluding those with Group III—paretic formula—fluids) and to the majority of those with late diffuse meningovascular neurosyphilis

4. Subdural treatment. The technique of this method is described in Chapter XXIII. It is rarely suitable as the sole method of attack, but is usually employed in conjunction with and in addition to routine treatment with the arsenical preparations and heavy metals Treatment is given not oftener than every two weeks on the alternate week an arsenical drug is given intravenously Thus while a course of 6 subdural treatments is being given, the patient will receive 12 intravenous injections, 6 of which are in conjunction with the subdural treatment, 6 on the alternate week. The interim of at least 3 months between courses is occupied by weekly intra muscular bismuth

The indication *par excellence* for this form of therapy is primary optic atrophy (see Chapter XX) in which subdural treatment should be given as soon as fever therapy has demonstrated its inefficacy To such patients two full courses of subdural injections (12 treatments) will usually suffice either to accomplish the desired result of arrest of the atrophic process or progressive visual failure during treatment will indicate its futility and the necessity of abandoning it in favor of possible surgical exploration for optochiasmatic arachnoiditis (cf p 325) When the method is used for the relief of lightning pains a few injections sometimes only two or three, will provide relief The C C G (O'Leary and others) is more impressed with the value of subdural treatment in neurosyphilis in general and especially in tabes dorsalis than ourselves.

Aside from its use in tabes we do not believe that subdural treatment has any advantage in other forms of neurosyphilis over less risky less painful and less expensive methods It is futile to expect any result whatever from it in paresis and we are opposed to its use for the sake of attempting serologic reversal only Its dangers especially in unskilled hands, are sufficiently great to justify it only when the possible therapeutic gain is adequate.

5. Tryparsamide. This drug and its method of use are described in Chapters VI VII and XXIII

In our hands, its greatest field of usefulness is as post-fever therapy in paresis in patients with other types of neurosyphilis whose spinal fluid abnormalities are resistant to other forms of treatment and as a general tonic and alterative (in the old pharmaceutical sense) in all types of neurosyphilis. In paresis it may be utilized when fever therapy is not available or is contra-indicated with better results than from any other form of chemotherapy (42 per cent remissions according to Solomon and Epstein) and in such cases should be employed from the start of treat ment In other forms of neurosyphilis it is our usual practice to withhold

tryparsamide until a six months trial of the arsenical drugs and heavy metals has demonstrated their inability to effect symptomatic or serologic improvement. The risk to vision, while small, is sufficiently great to justify the use of this drug only when less dangerous methods will not bring about results Finally tryparsamide is a particularly valuable drug in two classes of patients who cannot be given the arsphenamines in therapeutic dosage i e. arsphenamine-sensitive (dermatitis) patients and neurosyphilitic patients with associated cardiovascular syphilis. It is contra-indicated only in patients with partial optic atrophy

TABLE 85

SUGGESTED CORRELATION OF GENERAL SCHEME OF TREATMENT WITH APPROPRIATE TYPE OF NEUROSYPHILIS

Type of treatment (see text)	Useful in type of neurosyphilis indicated
"Routine"	"Minimal neurosyphilis early or late asymptomatic neurosyphilis with minor fluid changes late neurosyphilis with minor neurologic signs and negative spinal fluid some cases of vascular neurosyphilis.
Mild routine	Vascular neurosyphilis when complicated by aortitis, some tabetics as tonic treatment in elderly patients.
Intensified routine	Early meningeal neurosyphilis early or late asymptomatic neurosyphilis with moderate fluid changes most cases of late diffuse meningovascular neurosyphilis.
Subdural	Primary optic atrophy tabetic or otherwise in tabes for relief of lightning pains or ataxia.
Tryparsamide	All types of neurosyphilis with resistant spinal fluid serology (except optic atrophy) especially in paresis as follow-up treatment of malaria.
Fever	Paresis primary optic atrophy other types of neurosyphilis with persistent symptoms or resistant serology

6. Fever therapy This is described in detail in Chapter XXIII

Fever therapy is the ideal method at present available for the treatment of paresis and primary optic atrophy and in these conditions it should be employed as the first feature of treatment. Recent experience to be discussed presently indicates that it is also of value in other forms of neurosyphilis but our personal feeling is that, so far as the general practitioner is concerned and except in paresis or optic atrophy other methods of treatment should receive prior consideration. In the hands of the expert, and with a proper selection of patients the risk of fever therapy is minimal but there is a risk which in the hands of the inexperienced physician is magnified many fold.

These various indications for the application of different treatment schemes are briefly summarized in Table 85

The choice of drugs in the treatment of neurosyphilis — Much experimental work has been done as to the penetrability of one or another arsenical or bismuth preparation into the nervous system, and the use of this or that product urged because it appeared in the spinal fluid in somewhat larger traces than some other All this work is confronted, as we have already pointed out with the technical difficulties of accurate estimation of minute quantities of drug and is subject to criticism because of its assumption of the accuracy of several as yet unproved hypotheses. The predictions made in the laboratory as to the possible special value of drugs in neurosyphilis, as for example with sulpharsphenamine and silver arsphenamine have not been borne out by the rigid test of clinical practice. So far as the arsphenamines and heavy metals are concerned there are as yet no laboratory methods available which suggest the especial suitability of any one of these products in neurosyphilis. A choice must be based on the results observed in the clinic.

On clinical grounds, it seems to us that in neurosyphilis the arsphenamines may be rated in order of their relative efficiency as follows arsphenamine silver arsphenamine neoarsphenamine, and sulpharsphenamine. The last named is as we havé elsewhere stated, barred from use in adults because of its increased tendency to cause serious reactions. Neoarsphenamine seems in our experience to be far inferior to arsphenamine or silver arsphenamine in all types of neurosyphilis and we employ it only when relatively mild therapeutic effect is desired. Neither we nor others have accumulated enough experience with mapharsen in neurosyphilis to permit assigning a relative ranking. As to heavy metal preparations, we are not convinced that any one has any advantage over others, and see no reason for deviating from the routine use of for example, bismuth subsalicylate. It is true that laboratory studies originally suggested the possibility of use of tryparsamide in neurosyphilis and indeed it seems probable that further progress in this particular field of chemotherapy lies with the pentavalent rather than the trivalent arsenicals. The experimental work of Raiziss and Severac* has suggested the use of another pentavalent drug acetarsone (stovarsol) in neurosyphilis This preparation has been tried clinically by Griggs and Schamberg, Spiegel, Sézary and Barbé and others with satisfactory results. However reports concerning its use are still too meagre to permit its evaluation.

The Economic Aspects of the Treatment of Neurosyphilis as Affecting Methods of Treatment

Stokes and others have added to their treatment plans such procedures as the daily intravenous injection of soluble mercurial salts or of sodium

* The ingenious but as yet unconfirmed experiments of Raiziss and Severac are based on the discovery by Kolle and Schlossberger that a strain of *T pallidum* can be made to take on the neurotropic ability to penetrate the rabbit brain by means of preliminary passage through mice. In rabbits infected with such a strain of virus, the penetrability into the nervous system of various drugs may be studied by the sterilization of brain tissue, or its absence in treated animals.

iodide in an effort to intensify therapeutic efficiency However in most instances patients with neurosyphilis are ambulatory need not be hospitalized for long periods of time and in order to finance their living expenses and the cost of treatment desire to remain at work or to be restored to it as promptly as possible Therapeutic procedures calculated materially to increase the amount of time lost from work or the expense of treatment should not be considered unless the therapeutic gain is commensurate with the increased cost. In our experience the daily injection of drugs of any sort in the treatment of syphilis is not worth what it costs and such methods are in general applicable only to those patients who must be hospitalized for some other reason The physician must bear in mind that treatment for neurosyphilis is of necessity more prolonged and more expensive than for any other type of syphilitic infection He should do his best to keep his plan of treatment as simple as possible

The Treatment of Asymptomatic Neurosyphilis (Early or Late)

It is fair to assume that in early asymptomatic neurosyphilis the reaction produced within the neuraxis is largely inflammatory and limited to the meninges than when the fluid changes are discovered late in the infection. *A priori* therefore the results of treatment should be better in early than in late cases Actually this does not seem to be true. In our own material serologic reversal and freedom from clinical progression are as readily obtained late as early and the application of treatment methods need not differ appreciably with the duration of infection.

Patients with Group I fluids (***minimal abnormalities***) —When lumbar puncture discloses a slight to moderate pleocytosis and protein increase, with Wassermann and colloidal curves negative no special alteration of the treatment plan already in use for early or late syphilis is necessary Routine treatment with alternating courses of an arsphenamine or mapharsen and a heavy metal seems to accomplish satisfactory results in practically all instances and it is rarely necessary to resort to more drastic procedures However it is essential to prolong treatment on the average for at least 6–12 months longer than in the uncomplicated case. The duration of treatment is controlled by means of spinal fluid study carried out at least as often as every 6 months and regardless of the results of serologic tests of the blood treatment should not be discontinued until the spinal fluid has been completely normal for one year

Patients with Group II fluids (***moderate abnormalities***) — For this type of asymptomatic neurosyphilis early or late the intensified routine plan of treatment usually produces satisfactory clinical and serologic results This plan should be given a trial of at least 6 months at the end of which time the fluid should be retested. The criterion of serologic improvement is reduction of the titre of the serologic tests of the fluid reduction in cell count and protein content occurs so uniformly that it cannot be regarded as an indication of the ultimate value of the plan of treatment If there is definite improvement the same routine of treatment may be followed if not, or if at any later subsequent semi-yearly examination the improvement ceases at a level short of complete normality of the

fluid tryparsamide should be employed In the majority of instances the prolonged use of this drug in alternation with the arsphenamines and heavy metals will produce results. In the resistant cases, fever therapy should, we believe always be employed before treatment is finally stopped. It is unnecessary however if prompt serologic reversal is obtained and maintained The average duration of treatment necessary to accomplish satisfactory results in this group of patients is 2–2½ years

Patients with Group III fluids (the paretic formula) —Prolonged experience has shown that in this group of patients routine treatment with the arsphenamines and heavy metals will not bring about serologic reversal either rapidly or slowly Moreover the ultimate prognosis in such patients is so much graver than where fluid changes are less intense that more drastic treatment measures should be resorted to from the start. Our personal preference is for fever therapy either at once as soon as the fluid changes are discovered or as soon thereafter as the patient can arrange it. Following fever therapy treatment is carried on with tryparsamide and bismuth just as in paresis (pp 447–448) If fever therapy cannot be undertaken at once, tryparsamide should be used to fill in the interim. Even with the use of fever and tryparsamide, a complete guarantee of clinical safety for the future is not obtained progression may occur and should be carefully watched for Complete normality of the spinal fluid is likewise achieved in a smaller proportion of cases than in other types of asymptomatic neurosyphilis

In this type of case fever therapy as prophylaxis against the future development of paresis is desirable in every patient at some time during the period of treatment. We feel much safer about the future if this is done, as later comments (p 418) will indicate.

The average total duration of treatment in patients in this group will be at least 3 years indeed this amount of treatment should be regarded as the irreducible minimum.

Summary of treatment results in asymptomatic neurosyphilis —Utilizing the methods of treatment outlined above the percentage probability of clinical arrest, serologic negativity and of combined excellent clinical and serologic results in asymptomatic neurosyphilis is presented in Table 86. These data represent the results observed in some 400 well followed patients in the Johns Hopkins material.

Subdural treatment in asymptomatic neurosyphilis —Certain workers, especially Wile and the late J A. Fordyce have utilized subdural treatment in most patients with asymptomatic neurosyphilis. In our hands the results were not materially better with than without the addition of this procedure to the treatment plan. The cost of such treatment is enormously increased the danger of lower cord reactions mild or severe ever present. We do not believe the method justified.

Fever therapy in asymptomatic neurosyphilis —Numerous observers abroad (results up to 1927 summarized by Matuschka and Rosner) and O Leary in this country have treated asymptomatic neurosyphilis with malaria. This was originally done in the Vienna clinic shortly after the demonstration of the value of malaria in paresis as an experimental

TABLE 86
THE RESULTS ATTAINABLE BY TREATMENT IN EARLY AND LATE ASYMPTOMATIC NEUROSYPHILIS

Type	Percentage probability of		
	Clinical arrest	Serologic negativity	Combined clinical and serologic "cure"
Group I—fluid changes minimal	100	95–100	95–100
Group II—fluid changes intermediate	95–100	90– 95	90– 95
Group III—fluid changes maximal	60– 90	40– 60	30– 50

effort to study its effect in early syphilis. The usual plan of treatment abroad was (and in some places still is) two short courses of neoarsphenamine separated by an interval during which malaria was given. The early reports were highly favorable, not only in asymptomatic neurosyphilis but in early syphilis generally. Subsequent follow-up of such patients however has shown a high incidence of early infectious relapse (Kerl) and so far as patients with early syphilis and normal spinal fluids are concerned the scheme has been generally abandoned. In asymptomatic neurosyphilis, the foreign observers report a very high percentage of serologic reversal to normal of fluid abnormalities amounting in some reports to 100 per cent. This has not been confirmed by O Leary whose percentage of reversals during an average observation period of 1–9 years was only 44 per cent. More favorable results are reported by Wile and Hand 95 per cent of whose patients have remained clinically well over a period of 1–10 years. Reversal of the spinal fluid to normal, however occurred in only 20 4 per cent.

Our own feeling as to fever therapy in asymptomatic neurosyphilis is that it is seldom necessary except in patients with Group III fluids. The probability of satisfactory results from less strenuous measures is too high, and the risk of malaria too great to justify its general application. Its use is limited in our clinic, to patients with Group III fluids and to those of other groups in whom at least 18 months of other forms of treatment has failed to effect serologic reversal. Even in patients with Group III fluids malaria should not be employed if the infection is recent, until the patient has had at least 6 months' treatment with the arsphenamines and heavy metals, given for treponemicidal effect. Otherwise the probability of infectious mucocutaneous relapse is high.

We agree with O Leary however as to the prophylactic value of induced malaria in preventing the development of paresis in patients with asymptomatic neurosyphilis (especially Group III). Our combined series of patients so treated now numbers about 200 and in not a single instance has the development of paresis been observed

The Treatment of Early Meningeal Neurosyphilis* (Including Neurorecurrence)

In early meningeal neurosyphilis, whether occurring spontaneously or as a neurorecurrence, the desideratum of treatment is treponemicidal effect applied as powerfully as possible. Arsphenamine (606) is the arsenical drug of choice, to be given at the start of treatment. Herxheimer effect (therapeutic shock) need not be feared the initial dosage may be 0.3–0 4 gm. rapidly raised, if desired, to a maximum of 0 6 gm. For immediate symptomatic effect, we usually give 0 4 gm. every 4–5 days to a total of 12 injections in the first series. Combined with this should be given potassium iodide by mouth in large doses (6–20 gms. daily) and if the patient is sufficiently ill to justify hospitalization daily intravenous injections of

TABLE 87

THE RESULTS OF TREATMENT IN EARLY MENINGEAL NEUROSYPHILIS

Observer	Number of cases	Percentage obtaining "cure" or arrest		
		Clinical results	Serologic results	Combined results
Moore J. E.	54	83	62	62
Stokes and Shaffer	66	82	84 5	90
Fordyce	19	100	89	85
Merritt and Moore, M.	25	84	84	84

mercury succinimide, 0 01 gm. may also be used. If the physician wishes to be especially cautious as to possible therapeutic shock (though in our experience this is not essential) he may start with 0 1 gm. arsphenamine, increasing by 0 1 gm. every other day until a therapeutic dose is reached.

The immediate symptomatic effect of this sort of treatment is usually dramatically prompt. A seriously ill patient will be transformed into an apparently normal person within a few days. Cranial nerve lesions (excepting those involving the eighth nerve, to be separately discussed presently) clear up rapidly and completely Secondary optic atrophy following a neuroretinitis need not be feared. Except in rare instances, there are no permanent residuals when these occur they usually take the form of some dulling and blunting of the psyche or of the persistent remains of an associated vascular accident.

Further treatment by the intensified routine system brings about serologic reversal in from 60–80 per cent of the cases. The data shown in Table 87 (see also Table 82) represent the results obtainable by this method by several observers If complete serologic reversal is not ob-

* For a complete discussion of acute syphilitic meningitis the reader is referred to the excellent monograph by Merritt and Moore (Medicine 14 119, 1935).

tained after a year of such treatment tryparsamide should be employed and if results are still lacking 6–12 months later fever Neither tryparsamide nor fever therapy are advisable at the start of treatment however since with both these methods treponemicidal effect is far less than with the arsphenamines. Indeed in one patient with acute syphilitic meningitis in whom we inaugurated treatment with malaria, recurrent skin and bone lesions actually appeared toward the end of the fever paroxysms to disappear promptly as soon as arsphenamine was given.

It must not be forgotten that the ultimate prognosis of inadequately treated early meningeal neurosyphilis is grave. Among 32 such cases collected by Merritt and Moore (Table 82) 11 were arrested and 21 developed clinical neurosyphilis. In contrast arrest occurred in 51 of 59 adequately treated cases. Every effort should be made to persuade the patient to remain under treatment until blood and spinal fluid serologic tests have become and have remained negative for a full year, or failing this for an arbitrary minimum of 2½–3 years treatment which in the case of patients with resistant fluid abnormalities should include fever therapy toward its end.

The surgical treatment of meningeal neurosyphilis —Rarely the clinical picture of acute syphilitic meningitis may closely simulate that of brain tumor or brain abscess We have seen several patients in whom a neurorecurrence was associated with a large subdural hemorrhage over the convexity producing gradually deepening coma and advanced choking of the discs. In each of these patients decompression and evacuation of the clot seemed essential for the preservation of vision or life. Unnecessary operations in patients with acute syphilitic meningitis may be avoided, however if the neurosurgeon performs ventriculography to rule out brain tumor and at the same time counts the cells of the ventricular fluid A high count predominantly of lymphocytes should postpone operation until the fluid Wassermann can be done.

The Treatment of Vascular Neurosyphilis

The physician s problem on being confronted with a cerebral vascular accident in a syphilitic patient is to decide first whether the lesion is due *to syphilitic cerebral endarteritis or to some other cause particularly to* the combination of cerebral arteriosclerosis and hypertension second if presumably due to syphilis whether the lesion is primarily vascular or is associated with the paretic type of parenchymatous involvement. The abrupt onset of paresis with a *focal* vascular accident is by no means rare A decision as to these two points is often extraordinarily difficult but is important to attempt because of their bearing on treatment. Physical ophthalmologic neurologic psychiatric and serologic examinations are all essential. It must be recalled that even when the endarteritis is indubitably syphilitic the spinal fluid may be normal and unless the lesion is associated with paresis, the fluid usually shows only moderate abnormalities

When vascular neurosyphilis occurs in more or less pure form it is frequently associated with cardiovascular involvement as well. In this type

of neurosyphilis there is grave danger of a Herxheimer reaction (therapeutic shock) from the use of an arsenical drug at the start of treatment. Edema and increased cellular infiltration about an already involved cerebral or coronary vessel may do irreparable harm. The patient should be in bed at complete rest for the first *few* weeks of treatment, which should be begun with a heavy metal (bismuth intramuscularly or mercury by inunction) and potassium iodide in large doses. At least 10–12 weeks of preparation by this means should be carried out before the use of the arsphenamines is attempted. When an arsenical preparation is begun, it should be in minute dosage (e.g 0 1 gm. neoarsphenamine or 0 01 gm. mapharsen) cautiously increased as in cardiovascular syphilis. The ultimate dosage to be reached depends on the possible association of cardiovascular syphilis and its type if aortic regurgitation or aneurysm is present, a dose of 0.3 gm. neoarsphenamine or 0 04 gm. mapharsen should not be exceeded. If there are no evidences of an associated aortic lesion the average dose of these drugs may ultimately be reached without risk. Further treatment is carried on by alternating courses of an arsenical drug and a heavy metal much in accord with the outline suggested for cardiovascular syphilis and for a minimum duration of two years regardless of serologic progress

The ultimate results in this type of patient are only fair Our experience is in accord with that of Stokes and Shaffer who report only about 33 per cent of good results. Improvement from the immediate attack may occur but further cerebral accidents are almost the rule A crippling or fatal attack may occur even while the patient is actually under treatment and apparently doing well or it may follow the original attack and seeming recovery by an interval of many years. Even in those patients who respond most favorably to treatment, some degree of residual weakness, resulting in permanent handicap may remain

When the vascular lesion is associated with paresis, a totally different method of attack is used. The treatment system suggested above is useless in such cases the patient is faced with progressive parenchymatous change mental deterioration and death, unless more drastic measures are adopted. Immediately after the cerebral accident, a few weeks of preparatory treatment with bismuth and potassium iodide will aid in recovery from the vascular lesion but as soon as apparent improvement from this has become stabilized, malaria, or failing this tryparsamide should be given at once The risk from fever therapy is materially greater than in patients without focal lesions but in view of the gravity of the situation must be accepted. Subsequent treatment should be carried on as for paresis

Transverse myelitis Spastic paraplegia —These lesions are predominantly vascular due to thrombosis of one or more important spinal vessels, with or without a widespread meningomyelitis Though they may occur both early or late in the course of syphilis they are predominantly lesions of early syphilis (Berman) in which case the onset is generally acute. In late syphilis a more insidious onset is the rule. Treatment should be started with a heavy metal (therapeutic shock) but after a few weeks may be continued with arsphenamine. Chung's report is the best available

in modern literature. In reporting 34 acute cases he says Our statistics show death in six cases in only seven a condition worse on discharge than at entry and in twenty-one a varying degree of improvement from return of all sensation and reflexes to regaining of considerable motor power and sphincter control. The rapid recovery in some of our cases, I believe cannot be entirely attributed to the administration of arsphenamine or mercury but largely to the re-establishment of the blood supply of the depleted areas of the cord.' This coincides with our experience.

In chronic cases, with complete paralysis of lower extremities and sphincters, bed sores may be very troublesome and demand expert nursing care.

The Treatment of Late Diffuse Meningovascular Neurosyphilis

The diversity of clinical pictures presented by patients in this group makes it impossible to do more than to generalise as to methods and results. For the average patient complaining of "stomach trouble root pains headache loss of libido, cranial nerve palsies (except involvement of the optic or auditory nerves for which see below) convulsions etc. and showing on examination neurologic signs indicating diffuse involvement of the nervous system, primarily inflammatory rather than degenerative (without psychiatric changes indicating the presence of paresis), we usually start treatment by the 'intensified routine method. In spite of the fact that vascular involvement is common from the pathologic stand point clinically one rarely sees therapeutic shock as a result of starting treatment with an arsenical drug We regard the Herxheimer reaction as important only when clinical evidence of vascular involvement, as in transverse myelitis and spastic paraplegia, is obvious. Except in such instances, preparatory treatment is omitted

Immediate symptomatic relief during the first arsenical course (preferably arsphenamine or silver arsphenamine) is the rule. Whether the intensified routine system of treatment is continued depends not so much on symptomatic relief as on the presence or absence of serologic improvement at the end of 6 months of treatment. If the spinal fluid findings have changed appreciably for the better the same plan is continued for another 6 months If however improvement is lacking and particularly if the fluid is of the paretic type, tryparsamide, fever therapy or both are introduced into the treatment picture as promptly as possible.

A summary of what may be expected in symptomatic improvement clinical arrest, and serologic negativity from the series of Stokes Fordyce, and Moore and Hopkins is presented in Table 88 The results are better from clinical than from laboratory standpoints but from both are surprisingly good. These are pre-fever therapy figures

Hopkins survey of the Johns Hopkins material indicates that in most patients with late meningovascular neurosyphilis it is necessary to include in the treatment scheme at some time subdural treatment, tryparsamide or fever therapy Results from these three methods of treatment were approximately equal but the chance of clinical arrest and serologic negativity was nearly double that obtained from prolonged treatment with

TABLE 88

THE RESULTS OF TREATMENT IN DIFFUSE MENINGOVASCULAR NEUROSYPHILIS

Observer	Number of cases studied	Percentage probability of excellent or good		
		Clinical results	Serologic results	Combined results
Moore Hopkins	241	80	60–65	70
Stokes and Shaffer	94	83	76 6	74 5
Fordyce	139	76	43	?

the arsphenamines and heavy metals alone. *Excellent to good results* may be obtained in about 80 per cent of patients

Fever therapy in meningovascular neurosyphilis—Various observers in this country (Ebaugh Wile and Davenport, Wile and Hand Menagh, Kroll Bennett and Lewis and O'Leary) have used fever in the treatment of meningovascular neurosyphilis. With the exception of O Leary who feels that it is of little or no value, satisfactory results ranging from 58–83 per cent have been reported by other observers. Although fever and chemotherapy were combined in the majority of cases reported there is no doubt that the combination was productive of better results than from chemotherapy alone. We feel, however that in late meningovascular as in early or late asymptomatic neurosyphilis, malaria ought to be *reserved until at least a year's trial of other methods including* tryparsamide has demonstrated failure to bring about serologic improvement. The risk of death from meningovascular neurosyphilis is small as compared with that from paresis. It is wise, therefore, to try first those treatment methods which in themselves involve little or no risk. We agree that if the patient fails to improve and especially if the spinal fluid shows the paretic formula fever therapy should be given as prophylaxis for the future, at some time before treatment stops.

The treatment of primary optic atrophy occurring as part of meningovascular neurosyphilis—In a considerable number of patients primary optic atrophy occurs in patients who present no signs of the posterior column involvement of tabes other symptoms and signs may instead be those usually associated with basilar meningitis. It has been held by some workers that the prognosis for arrest of the atrophic process is better in this than in the tabetic type of optic atrophy In our material, such a prognostic differentiation is not apparent. The prospect of complete blindness if the patient is untreated or treated by inadequate methods, is as great in one type as in the other Only two forms of treatment seem to be of any avail fever or subdural therapy and one of these should be adopted as soon as the diagnosis is made. Any other therapeutic efforts are usually completely useless in arresting visual failure and con-

stitute dangerous temporizing A more detailed consideration of the treatment of optic atrophy is provided in Chapter XX.

The Treatment of Auditory Nerve Involvement in Neurosyphilis

Involvement of the auditory nerve by syphilis may occur in conjunction with any type of neurosyphilis, i e acute syphilitic meningitis late diffuse meningovascular neurosyphilis tabes or paresis In congenital syphilis it appears apparently always as an isolated phenomenon without any other clinical or serologic evidence of involvement of the neuraxis Furthermore under either of these circumstances the lesion may select the cochlear or vestibular branches alone or may destroy the entire function of the nerve. The pathologic changes underlying the functional disturbance are not as yet well known even as to their exact location It is convenient to discuss the results of treatment of eighth nerve involvement in a single section including even those cases congenital or acquired in which the lesion is probably not associated with any intracranial inflammatory process

The patient is more largely incommoded by involvement of the cochlear branch resulting in partial or complete deafness than by loss of vestibular function. For the latter he can usually compensate in the course of time even if he is not treated the symptoms of vertigo nausea and vomiting and faintness, tend to disappear as destruction of the vestibular apparatus becomes complete Deafness however remains as a permanent handicap unless relieved by treatment.

Unfortunately most of the available information as to treatment results antedates the accurate measurement of hearing defects by the audiometer Experience with this instrument in our own patients has demonstrated that the patient s statements as to the acuity of his hearing must often be discounted sometimes he complains of deafness when objective tests show no hearing loss sometimes he thinks his hearing is normal when actually it is impaired Thus the accurate evaluation of the effect of treatment on the hearing defect demands the use of the audiometer The Johns Hopkins material has been recently studied in this manner and reported by Cloceo and Weinstein.

Striking relief from impaired hearing is usually obtainable only when the lesion is associated with early meningeal neurosyphilis (occurring as a neurorecurrence or otherwise) Here the development of the partial or complete hearing defect is often sudden the cochlear branch alone is often involved serologic findings usually demonstrate the association of the lesion with an acute inflammatory process in the meninges. In something more than half the patients so affected the prompt administration of intensive arsphenamine therapy results in a rapid improvement in hearing often to its original level. In the remainder there is either no improvement or some degree of permanent residual deafness persists

In the various forms of late neurosyphilis and in those instances of congenital or acquired syphilis in which the lesion appears as an isolated phenomenon improvement in hearing as a result of antisyphilitic treatment by any method excepting fever therapy is almost never obtained

Occasionally when hearing loss is only partial, its progress may be apparently arrested It is difficult to be sure however that arrest is due to treatment and not spontaneous, since the latter also may occur Often the lesion is progressive in spite of treatment and complete deafness results.

Neither in early late or congenital syphilis is there any evidence of therapeutic shock from treatment. We have never observed a sudden increase in deafness following the initiation of treatment with large doses of arsphenamine Curiously enough, though antisyphilitic treatment has little influence on cochlear lesions, it is stated by various German observers to relieve symptoms and to cause the improvement or disappearance of physical signs in about half the cases of vestibular involvement whether this occurs early or late. Our own data on this point are too incomplete to confirm this statement.

There are available reports in the literature (Krassnig Beck Memmesheimer and Theissing, Matuschka and Rosner) which although not

TABLE 89

RESULTS OF MALARIA THERAPY IN SYPHILITIC NERVE DEAFNESS
(From various observers—see text)

	Cases	Clinical outcome	
		Improved	Unimproved
Cochlear branch	27	11	16
Vestibular branch	30	17	13

controlled by careful study with the audiometer suggest that fever therapy (malaria) may be the method of choice in dealing with syphilitic involvement of the eighth nerve The observations of these investigators relating almost entirely to patients with late acquired or congenital syphilis are collated in Table 89 Some degree of improvement in hearing was noted following malaria therapy in 11 of 27 patients with cochlear lesions, and in most instances the benefit persisted over a period of months or years. As in reports of other treatment methods improvement in vestibular lesions was more easily secured (17 of 30 patients) Our own experience with fever therapy in this condition includes 20 patients (not included in Table 89), in none of whom was any objective benefit obtained. Nevertheless the method deserves a further trial in nerve deafness since otherwise the outlook for restoration of hearing (except in acute meningeal neurosyphilis) appears hopeless.

The Treatment of Tabes Dorsalis

It is necessary to discuss the treatment of tabes dorsalis from three points of view —first, the desirability in certain cases of giving treatment or withholding it completely second the gross results obtainable in large series of patients and third the relief of particular symptoms by special therapeutic methods.

In about 10 per cent of all tabetics spontaneous arrest of the degenerative process occurs In such patients, symptoms appear and progress for a period of several years then either spontaneously disappear wholly or in part, or remain in *status quo* for many years without evidence of further progress. Physical signs show little alteration during prolonged observation examination of the spinal fluid shows no significant abnormalities. This is the syndrome of so-called "burnt-out tabes The decision as to whether to treat such patients at all is often a very nice one. Instances are reported of which we have seen a few examples, in which treatment has seemed to stir up dormant symptoms and actually to promote rather than to check progress In general it may be said that treatment and its type in such individuals should be based more on possible evidences of syphilis outside the nervous system and particularly in the cardiovascular apparatus than on the neuraxis lesion In any event, intensive methods of treatment, especially subdural or fever therapy do not seem justified under these circumstances. If given at all, treatment should be mild, tonic, and prolonged (neoarsphenamine or mapharsen and heavy metals in moderate dosage only)

In about 90 per cent of tabetics, however treatment is obligatory either for relief of symptoms or arrest of progress. The type of therapy to be employed at the start depends partly on the patient s general physical status and partly on whether he suffers from either one of two particular manifestations of the disease, primary optic atrophy or gastric crises Assuming that neither of these conditions is present, that the patient is under the age of 55–60 that his general physical condition is satisfactory and that he does not also have well marked cardiovascular syphilis, only too commonly present, it is desirable to start treatment with the "intensified routine" system, and to carry it on for 6 months without additions or alterations. If symptomatic and serologic improvement are prompt this may be continued usually however while there may be benefit to the patient s general physical condition one or more distressing symptoms persist. The next step is to add tryparsamide to the treatment scheme remembering that particular precaution is necessary to avoid visual damage from the drug, the incidence of which is higher in tabes than in any other type of neurosyphilis (presumably because in so many tabetics the optic nerve is already affected by syphilis) At least a year's trial should be given to tryparsamide in combination with the heavy metals before abandoning hope of improvement from it. Whether or not clinical improvement is obvious at the end of this time, if serologic benefit is not evident fever therapy should be instituted. The total duration of treatment in any case should not be less than 2½–3 years.

If the patient is elderly if his general physical status is poor if he has an associated cardiovascular syphilis treatment must be much less intensive. Neoarsphenamine or mapharsen may be substituted for arsphenamine The interval between the arsenical courses is 3–4 months instead of 8–10 weeks to be filled wholly or partly by periods of mercury by inunction or bismuth intramuscularly Short rest periods are desirable.

Subdural treatment in tabes —Subdural treatment in tabes is par

ticularly useful from two standpoints —the relief of particular symptoms, especially optic atrophy lightning pains and ataxia and serologic reversal. So far as symptomatic relief is concerned the use and effect of subdural treatment is more fully discussed in subsequent paragraphs. Viewing our own material as a whole the general clinical result is but little better when intraspinal treatment is used than when it is not, but the percentage of serologic reversal or of combined excellent clinical and serologic results is more than doubled by its use.

The results of treatment—Stokes and Shaffer Fordyce, Moore and Hopkins and especially the C C.G, have studied the gross results of treatment in tabes in nearly 1,500 cases. These patients were thoroughly treated by all available methods including fever therapy and followed for years after treatment stopped. Excellent or good clinical results are obtainable without fever therapy (Table 90) in a little more than half the patients. The parallelism or lack of it between clinical and serologic outcome will be commented upon presently

TABLE 90

THE RESULTS OF TREATMENT IN TABES WITH CHEMOTHERAPY ALONE

Observer	Number of cases studied	Percentage probability of excellent or good		
		Clinical results	Serologic results	Combined results
Moore Hopkins	126	55–60	25–40	40
Stokes and Shaffer	170	63	67	48 3
Fordyce	150	40–50	22	51 3

Fever therapy in tabes—The reports of some investigators who have used fever therapy in tabes are enthusiastic others are more conservative. As a matter of fact, it is not yet possible to compare gross clinical and serologic results in a large series of fever-treated tabetic patients with those obtained by standard methods too few patients have been treated and too little time has elapsed since treatment. The C.C.G is not helpful in this respect since fever therapy when employed at all was always used in patients in whom less drastic methods had failed to produce satisfactory clinical or serologic results. Various observers have however reported *that malaria gives a higher incidence of improvement in certain* tabetic symptoms notably ataxia, lightning pains gastric crises and optic atrophy than standard methods. This information summarized from about 50 cases reported by Berling, Dreyfus and Hanau Hoff and Kauders, Ebaugh, and Wile and Davenport appears in Table 91 We have treated about 70 tabetics with malaria, without such spectacular success as these results indicate In our hands, ataxia, if marked before is usually worse

TABLE 91

IMPROVEMENT IN SYMPTOMS OF TABES FROM STANDARD METHODS OF TREATMENT AND FROM MALARIA

Symptoms of tabes	Percentage of improvement with	
	Standard methods	Malaria
Ataxia	20–30	70
Lightning pains	40–60	74
Gastric crises	20–30	80
Optic atrophy	—	—

See Chapter XX.

after treatment. We have had several disastrous experiences in attempts to utilize fever in tabetics with cord bladders. Complete bladder paralysis, catheterization cystitis, and ascending urinary infection are to be especially dreaded

Nevertheless on the basis of our present information there seem to us to be several definite indications for the use of malaria in tabes as follows (1) as the initial step of treatment in all patients with obvious taboparesis (2) in patients with optic atrophy the progress of which is progressively downhill in spite of subdural treatment (3) as treatment for gastric crises unrelieved by other means and before resorting to surgical procedures (4) in any tabetic patient whose spinal fluid findings of the paretic type, are resistant to prolonged standard treatment. Except for these indications we think it wiser to avoid the risk to life which malaria involves

The treatment of certain tabetic symptoms Ataxia —When the development of ataxia is slowly progressive relief from standard methods of treatment is obtained in only about 20 per cent of cases. This may be improved to about 30 per cent by the use of subdural treatment. Though improvement may be lacking intensive treatment may stay the progress of the posterior column degeneration in a majority of patients Occasionally a patient is encountered in whom the onset of severe ataxia is very sudden even within 24 hours In such individuals the prognosis from standard treatment is good

If the patient is seriously handicapped by his ataxia, an attempt should be made to persuade him to undertake methods of re-education Frenkel s elaborate monograph supplies detailed instructions as to suitable exercises By means of re-education astounding results may sometimes be accomplished. We have seen an individual so ataxic as to be unable to stand without support, transformed into one with an almost normal gait requiring not even the aid of a cane Unfortunately exercises are difficult for the patient to carry out alone the expert cooperation of a trained physiotherapist is almost essential. This places the method beyond the financial reach of most tabetics. Given the ability to pay for re-education success depends largely on the patient his dismay over slow progress must

be met with encouragement he must be willing to devote hours daily to graduated exercises and he must face the necessity of prolonged training lasting several years.

Lightning pains —Both physician and patient should know that almost any therapeutic efforts—an injection of arsphenamine, an intra spinal treatment, fever—will cause a temporary and sometimes violent exacerbation of lightning pains. This is true of acute or chronic intercurrent infections as well sometimes pains refractory to all forms of antisyphilitic treatment improve as a result of removal of an abscessed tooth or of chronically infected tonsils. The patient should be warned that treatment of any sort will probably not relieve this symptom completely the best that can usually be hoped for is to decrease the frequency and severity of attacks. Apparently pain may persist as a sequel of scarring and degeneration in the dorsal roots, long after the acute inflammatory process has subsided.

In about half the patients treated, a considerable degree of relief is obtained from intensified routine treatment. Among the remainder especially if attacks are so frequent or so severe as to incapacitate the patient, subdural treatment first, and later fever therapy if necessary will often prove effective. A long course of subdural treatments is neither necessary nor desirable benefit, if any will be obtained from 3 or 4 intraspinal injections at 2 weeks' intervals.

Halpern and Kogerer offer the interesting observation that during bouts of lightning pains (or attacks of gastric crises) there may be slight elevation of the blood sugar level (to about 135 mgms. per cent) that the pain may be due to unusual sensitivity of nerve tissue to this concentration of sugar and that symptoms may often be promptly relieved by the administration of one or several injections of 5–8 units of insulin We have had no personal experience with this procedure.

Because the pathologic changes in spinal cords of tabetics are similar to those which may be produced in swine by vitamin B_1 deficiency and for various other theoretical considerations Metildi treated a small group of patients with lightning pains with 10–20 mgms. weekly of thiamin chloride with apparently satisfactory results. Kemp and Cochems* were unable to confirm Metildi's results although they administered much larger amounts of the drug. Recently however we have found it of great value when given in sufficiently large doses. We advise the parenteral administration of 100 mgms. daily for 7–10 days and 50–100 mgms. weekly thereafter In at least a dozen patients we have seen marked relief or complete disappearance of previously intractable lightning pains after the prolonged use of larger amounts of thiamin chloride.

Optic atrophy —The management of this complication is discussed in detail in Chapter XX

The cord bladder —Knowledge of the cord bladder has been greatly advanced by the experimental and clinical work of many investigators summed up in the recent monographs of McLellan and of Langworthy Kolb and Lewis. The latter workers say —

* Unpublished data.

We have examined the histories of 378 patients with tabes dorsalis seen in the Johns Hopkins Hospital. Abnormalities of micturition were mentioned in 140 incontinence occurred in 83 and hesitancy in starting micturition in 71 Nocturnal incontinence was a prominent symptom in 22 patients. Frequency is a manifestation of overflow incontinence The vesical symptoms found in tabetics are dependent on loss of knowledge of bladder distension due to injury of the sensory nerve fibers. The decreased tone of the muscle which follows an interruption of the primary reflex arc is exaggerated by stretching of the wall Poor tone and contraction of the muscle causes slowness in initiating micturition and loss of strong expulsive force. Dribbling occurs at the end of micturition because of the fact that the bladder contraction is incomplete. Since the muscle does not contract to expel all of the urine, a residuum gradually collects. There is some actual evidence of disturbance of sensation in the bladder wall

Cystoscopic examination reveals relaxation of the internal vesical sphincter funneling of the prostatic urethra, and a smooth pale bladder wall with fine trabeculation.

In the urologic management of the tabetic bladder prevention of infection or its treatment if present is the most important aim. Instrumentation should be avoided unless it becomes absolutely necessary Patients should be urged to empty the bladder frequently and regularly Since they no longer feel the discomfort of vesical distension they neglect to attempt micturition except at long intervals. The accumulation of urine stretches the vesical wall severely and leads to atrophy of the muscle producing progressive disability "

Acetyl-beta-methyl-choline (mecholyl) is particularly useful in the treatment of the tabetic bladder This drug stimulates the parasympathetic nerves and causes contraction of the bladder wall. It is given by mouth, 200–300 mgms. daily in divided doses

The problem of the cord bladder in syphilitic transverse myelitis, including Erb s spinal spastic paraplegia, is of a somewhat different character In this respect we paraphrase slightly from McLellan

The result is complete atony with overdistension and overflow Three methods of treating this situation are at hand (a) to do nothing and allow the bladder to overflow until that time when its reflex activity is re-established, which allows for periodic evacuation (b) immediate suprapubic drainage and (c) the inlying urethral catheter with intermittent irrigation (the latter is the method recommended by McLellan) There is conflicting testimony as to the value of mecholyl in cord bladders of this type.

Infection of the bladder with possible spread to the upper urinary tract may also be adequately controlled by the use of sulfonamide compounds and mandelic acid.

By means of cystometric studies, Lewis and Langworthy have shown that not only are bladder disturbances one of the earliest signs of tabes but that in the majority of instances they can be detected before the development of even minor urinary symptoms. Moreover they have found it possible to differentiate between the posterior column involvement of

tabes and involvement of the corticospinal tracts consequent to other forms of neurosyphilis The interpretation of cystometric abnormalities in neurosyphilitic patients who are entirely asymptomatic is occasionally difficult however since abnormal readings similar to those encountered in tabes are sometimes encountered in normal individuals (Boyd and Smith) The great value of cystometry is that it permits the early recognition of the tabetic bladder (Brodie, Helfert and Phifer) and in many instances its differentiation from other bladder disturbances particularly those caused by obstruction The combination of obstruction from prostatic (often median bar) hypertrophy and the cord bladder is one which requires expert urologic evaluation and surgical relief of obstruction when present.

Antisyphilitic treatment of the cord bladder and results — Before starting antisyphilitic treatment, a careful study of renal function should be made. If there is evidence of renal insufficiency (low phthalein, nitrogen retention) treatment should be withheld until urological treatment has lessened the residual urine and controlled the back pressure.

Treatment should begin with an arsphenamine or mapharsen which together with heavy metals and potassium iodide should be employed for at least 4–6 months before other measures are attempted. Subdural (intraspinal) treatment, if considered at all should be given only by an expert. We have seen the injudicious use of this method result in complete paralysis of a previously only partially damaged sphincter If arsphenaminized serum is given subdurally it should be started with minimal doses (2–5 cc. of serum well diluted with spinal fluid) and under no circumstances should treatments be given oftener than every 2 weeks

Routine intensive treatment, together with adequate urologic cooperation, is responsible for marked improvement in about one-third of the cases. In the remainder improvement is slight or absent.

Fever therapy must be undertaken with great caution in patients with cord bladders. Acute retention during the fever almost invariably occurs, necessitating catheterization with its dangers of infection. We have seen several deaths from this cause in the early days of malaria therapy before the relative contra-indication was recognized The contra indication to the use of malaria is only relative however other features of the patient s illness may render fever therapy imperative In this case, constant urologic and medical cooperation may succeed in getting the patient through without serious difficulty Additional relief may follow the administration of ergotamine tartrate (Palmer and Gernon) or mecholyl (Lovin)

Charcot joints —Among 744 tabetics observed at the Johns Hopkins Hospital, Charcot joints developed in 6 per cent. Our experience corresponds with that of Wile and Butler who noted "the large number of cases in which the condition occurred in apparently stationary or arrested cases of tabes Few of our patients showed any marked symptoms of tabetic disease such as root pains crises optic atrophy or other symptoms of cord disease and singularly few sought the hospital for symptoms referable to central nervous system disease the vast majority seeking relief from the joint symptoms. Indeed we have even observed the develop-

ment of Charcot joints in thoroughly treated and apparently arrested tabetic patients years after other evidences of progress had ceased and while the laboratory findings in blood and spinal fluid remained normal Other patients under active treatment because of one Charcot joint have developed a second or even a third arthropathy actually during treat ment.

Not only are other evidences of progression in the nervous system (ex cept the arthropathy) usually lacking but also serologic abnormalities in blood and spinal fluid are present much less frequently than in tabetics without Charcot joints In our experience 40 per cent of patients with tabetic arthropathies have normal spinal fluids while this is true of only 20 per cent of tabetics with normal joints.

These facts have a definite bearing both on the mechanism of development of the Charcot change and on the rationale of treatment. The com monly accepted theory of the etiology of tabetic arthrophaties is well stated by Wile and Butler 'In every instance the joints involved are associated with destruction of their afferent (proprioceptive) nerves rendering them unable to compensate for injury With each minor injury under these con ditions or with trauma which might be considered physiologic further deviation in the structure of the joint occurs resulting ultimately in the accumulated pathologic change which makes up the end picture of Char cot s joint. The primary factor therefore would appear to be the inability of the joint to compensate for injury dependent on spinal cord disease while the contributing factors are the various forms of insult to which a thus predisposed joint is exposed. This theory fits well with the observed preponderance of involvement of the joints of the lower ex tremities

The antisyphilitic treatment of patients with Charcot joints — Since the primary factor in the development of tabetic arthropathies is destruction of the afferent nerve fibres from the joint (in the dorsal col umns of the spinal cord) it follows that unless antisyphilitic treatment can restore destroyed nerve tissue very little benefit to the joint process is likely to occur This is actually the case In an experience covering about 200 patients with Charcot joints, we have seen improvement apparently resulting from antisyphilitic treatment only once. In the others, any drugs in any combination and by any route (including the subdural) and fever therapy in various forms have been without effect. Whether or not a patient with tabetic arthropathy should receive any antisyphilitic treatment and the form which this should take depends on other factors than the joint If there are other symptoms of actively progressing tabes such as lightning pains ataxia, sphincter disturbances, or optic atrophy or in the absence of these if the blood serologic tests are positive the cerebrospinal fluid abnormal or both or if as frequently occurs an associated cardiovascular syphilis is present the patient should be treated. If on the other hand the Charcot change appears in a patient whose neuraxis infection is apparently burnt out (duration of several years without other signs of progression serologic tests of blood and cerebrospinal fluid negative) or if it occurs in a patient who has already received several years

of treatment and who has not otherwise progressed, treatment may be more properly withheld. In any case treatment is given not so much because of as in spite of the Charcot joint.

The orthopedic management of Charcot joints —The orthopedic management of tabetic arthropathies is more important so far as the local lesion is concerned than antisyphilitic treatment. The Syphilis Division of the Johns Hopkins Hospital has been fortunate in having closely associated with it two able orthopedists, Key and Weinberg both of whom have published their conclusions as to orthopedic treatment. We quote extensively from Key's article which is partly based on further studies carried on at Washington University

> Treatment of the joint itself is divided into conservative and operative methods. Many of these joint conditions arise in senile individuals with tabetic bladders, arteriosclerosis, paralysis, and hemiplegia. These cases are not good operative risks and should not be operated upon because even if the operation is successful their general condition is such that they will not receive very much benefit from the procedure. On the other hand, fairly vigorous patients under sixty years of age and in a state of good general health can, in many instances, be benefited by surgical procedures and should be given the opportunity either to choose or reject the operation.
>
> Conservative Treatment.— The objects of conservative treatment are to reduce the pain and swelling and protect the joint from damage incident to use.
>
> An acute Charcot joint should be put at rest. Not only should weight bearing be forbidden, but the joint should be immobilized in a splint or plaster-of Paris cast. The cast can be bivalved and removed daily for physiotherapy The physiotherapeutic agents apt to be of most benefit are local heat (hot fomentations, infra-red rays, bakes, or diathermy) (care should be taken not to burn the skin which may be less sensitive to pain than normal) and exercise without weight bearing to aid the circulation and preserve the normal tone and power of the muscles of the extremity If the joint is distended with fluid this should be aspirated as often as necessary in order to prevent undue stretching of the capsule and ligaments.
>
> As the pain and swelling subside the patient will insist upon using the joint to the limit of toleration. The surgeon should keep in mind the fact that such a joint is abnormally vulnerable to injury and cannot be expected to survive the trauma incident to normal use. The surgeon should restrict the activity of the patient and should prescribe a suitable support in order that the vulnerable joint may be protected as much as possible. The mechanical support should be designed and fitted with unusual care as the patients are inclined to abuse the diseased joints and cannot be depended upon to judge as to the efficiency of the apparatus.
>
> Not only should the apparatus be carefully fitted, but it must be inspected at frequent intervals in order that it may continue to fit and be kept in satisfactory repair Not only must the apparatus be examined, but the skin of the patient must be watched in order to guard against pressure sores which may develop in areas of decreased sensation and lead to troublesome ulcerations.
>
> The type of apparatus varies with the joint and with the surgeon. For a Charcot spine a high back brace or a celluloid, leather or plaster-of Paris jacket should be fitted and this will make the patient much more comfortable and will usually render him ambulant again. A patient with a Charcot hip knee, ankle or foot should be fitted with a Thomas caliper walking splint. The ring of this

phate. In all there was prompt immediate relief which persisted in 7 instances for several months. The injection was usually followed in several hours by a paraparesis without sensory changes which cleared up in 24 hours. With this method of treatment we have had no experience

A report by Alajouanine and Horowitz details encouraging results both as to immediate and prolonged relief of gastric crises, by a method of treatment with which we have had only slight personal experience The treatment consists of the intravenous injection of 1–3 mgms. of atropine sulphate repeated once or twice daily for several days. Thirty patients were treated, some in whom the disturbances seemed predominantly vagal in others with sympathetic symptoms predominating Favorable results were almost constant, and in most patients the improved condition lasted a year or longer Why prolonged improvement should be obtained by a relatively short period of partial vagus paralysis is not clear but the authors are so enthusiastic that the method seems worth trial

Antisyphilitic treatment of tabes with gastric crises Methods and results —Since the treatment of tabetic patients especially those with gastric crises is likely to be a long drawn out procedure, it is our usual custom to start with the least drastic or dangerous methods of treatment, adding other drugs or procedures in the event of failure of improvement. In the usual patient with gastric crises therefore a start is usually made with intensified routine treatment, i.e. long courses of large doses of an arsphenamine or mapharsen interrupted by shorter courses of bismuth and potassium iodide. This will give symptomatic relief in an occasional patient. If as usually happens improvement does not occur subdural treatment (given intraspinally) is added. In about 25 per cent of all cases this results in lessening the frequency duration and severity of the attacks.

Should this be ineffectual, a few months' trial of tryparsamide may be worth while before resorting to still more drastic measures We have not been impressed by the results secured with tryparsamide in patients with gastric crises only an occasional patient showing improvement.

Fever therapy preferably with malaria, is the next step. This is effectual in providing some degree of relief to perhaps another 25 per cent of patients. From all these various methods, singly successively or in combination the physician may expect complete relief in 10 per cent of cases some improvement in about 40 per cent and no benefit in the remainder For these unfortunate persons surgical procedures offer the only remaining hope.

The operative treatment of gastric crises —We quote in part from Keidel

Operation for gastric crises is always a last resort. It should not be employed unless all available methods of medical treatment have been tried and proved unavailing, and unless attacks are becoming more frequent and more prolonged If as rarely occurs, severe attacks are almost continuous, operation may be the only alternative to starvation morphinism or suicide

Before attempting major surgical procedures, it may be well to observe the effect of paravertebral alcohol block, as proposed by Swetlow for the relief of

cardiac pain. This involves the blocking of the thoracic sympathetic chain and obviously should be attempted only by an expert. Baker has done it for me on three patients one of whom obtained complete relief from previously intractable crises. Its worth must be proved by further study

Various operations have been proposed and tried here and abroad The most important of these are—(a) posterior rhizotomy or section of the posterior nerve roots from the 5th to 12th thoracic segments. This operation is apparently successful in relieving symptoms in about 20 per cent of the patients subjected to it. (b) Since the cutaneous and deep anaesthesia produced by this operation is rarely as complete as one would expect on anatomical grounds, it has been repeatedly suggested that the anterior nerve roots almost certainly carry some afferent sensory fibres and that posterior rhizotomy to be complete, should include section of the corresponding anterior roots as well. This operation has the additional advantage of completely interrupting the sympathetic nerve circuit. (c) Section of one or both vagus nerves usually with gastro-duodenostomy or gastro-enterostomy to counteract the ill effects of paralysis of the stomach has been proposed and tried in a few cases with conflicting results. (d) The latest proposed operation is section of the antero-lateral columns of the spinal cord, usually in the lower cervical cord. This operation has proved of great service for other types of intractable pain as from malignant metastases in the spine or pelvis. The result of the operation is heterolateral loss of pain and temperature sense with persistence of light touch and deep sensation below the the level of operation. In gastric crisis, the section must be bilateral.†

All of these operative procedures have offered permanent relief in some cases and have failed miserably in others. Recently it has been suggested by various authors that the possible reason for the unpredictable success or failure may lie in a possible dual origin of the symptom of gastric crises that the crisis characterized by intense nausea and vomiting but without pain is vagal in origin, while that in which pain is the outstanding feature with nausea and vomiting subordinate or even absent, is due to involvement of the sympathetic system. This is a subject which needs much further study and to which the neurosurgeon can contribute by a careful selection of cases for operation. In the vagal type, the operation of choice may be section of the gastric branch of the vagus combined with gastro-enterostomy In the sympathetic type, chordotomy It must, however be remembered that in gastric crises, surgery is not only a last resort, but is still on an experimental basis.

The operation of chordotomy may also be tried in the case of severe and intractable lightning pains, though, fortunately, this manifestation of tabes is more easily relieved by appropriate antisyphilitic treatment than the gastric crisis, and even if not benefited, they are rarely so demoralizing and devastating in their effect on the patient.

Excellent discussions of the nerve pathways responsible for abdominal pain and for vomiting are provided by Alvarez. The subject is a most confused one and, as Alvarez puts it, 'Many difficulties remain to be over come and much needs to be learned about the possibilities and limitations and disadvantages of nerve sectioning. Great care will have to be exer

Several other patients have been treated more recently with relief in about 1 in each 4 cases. White of Boston has, however seen no relief (personal communication)

† This operation has been done for us by Dandy in 3 patients, none of whom were relieved. White, however reports two successful cases and Kahn and Barney excellent results in 8 of 12 cases.

cised in choosing patients for study or operation and good sense and con servatism will later have to enter into the judgments made as to the results of the treatment.

In patients with gastric crises unrelieved by antisyphilitic measures specific or non-specific and also unrelieved by bilateral alcohol block of the dorsal sympathetic chain, it begins to appear that pain (and sometimes vomiting) may be relieved permanently by anterior chordotomy (White 2 cases Kahn and Barney 8 of 12 cases Hyndman and Jarvis 8 cases) In patients in whom nausea and vomiting is the predominant feature bilateral vagotomy just below the diaphragm (an operation first proposed by Exner) has been found to provide relief in at least 11 of 18 patients followed for one year after operation (McCrea) In our personal experience the nausea and vomiting component in gastric crises has been much more troublesome than pain and further experience with vagotomy is urgently desirable

Loss of libido and potentia —This symptom often one of the earliest manifestations of tabes to appear is common in diffuse meningovascular neurosyphilis as well Its reaction on masculine pride is sometimes the cause of much mental difficulty Improvement in sexual function as a result of any method of treatment is infrequent (about 25 per cent) and is often only transitory Psychotherapy may be of value. Testosterone is of no avail.

The C C G study of the treatment of tabes dorsalis —The C C G has studied the outcome of treatment in 985 patients with tabes dorsalis. Briefly summarised their conclusions from the purely serologic standpoint are as follows

An accurate comparative appraisal of the numerical value of routine treatment, intraspinal treatment, malaria therapy and tryparsamide was not feasible in this material some pertinent facts, however were elicited about the four therapeutic procedures. The treatment of tabes must be individualized because in certain patients excellent results are obtainable after a few injections of arsphenamine and a heavy metal. In others the intensive use of chemotherapy and perhaps the addition of one or two of the supplemental measures is necessary to arrest the process while in some patients the intensive and prolonged use of the specific as well as the nonspecific methods will fail to control the disease.

In 60 per cent of a group of 266 patients who received only routine treatment, the spinal fluid became negative However of the 396 patients who were started on routine treatment in only 20 per cent was the spinal fluid reversed and of the group in whom reversal failed to occur 173 were given intraspinal therapy which was followed by serologic negativity in 53 per cent. In other words intraspinal therapy was successful in reversing the spinal fluid in more than one-half of those in whom routine treatment failed. In another group of 66 patients tryparsamide was successful in reversing the spinal fluids in 20 per cent after routine and intraspinal therapy had failed Malaria therapy was given to 75 patients after the other supplemental methods had failed and in 35 per cent of these the serology was reversed to negative. The value of the supplemental methods is further demonstrated by the fact that in 194 patients who failed to obtain serologic reversal from routine treatment the auxiliary measures were serologically

successful in 51 per cent. The majority of the reversals occur by the third year of treatment with the various treatment procedures with the exception of tryparsamide with which the maximum results are noted about the tenth year. If toward the end of the first year of treatment or after 20 injections of arsphenamine and twice as much heavy metal have been given and the spinal fluid is unchanged, the supplemental treatments should be given bearing in mind that intraspinal therapy will produce serologic reversals in about one-half the time that tryparsamide requires, and furthermore that malaria therapy will reverse the serology in one-third of the cases in which routine intraspinal therapy and tryparsamide have failed.

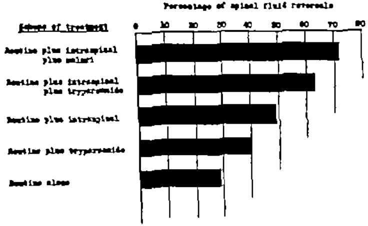


FIG. 76.—Effect of various treatment schemes upon spinal fluid reversal in patients with tabes dorsalis (from C. C. G.)

More important, however, are the clinical results:—

The best clinical results were noted in those patients in whom the manifestations of tabes were of recent appearance, in whom the syphilis was of less than 10 years' duration, and who obtained reversals of the blood and spinal fluid to negative. The less abnormal the spinal fluid the better were the clinical results, and to obtain successful results from routine treatment more than 20 injections of arsphenamine and twice as much heavy metal should be given. Of the 286 patients who received only routine treatment, clinical arrest appeared in 15.4 per cent, while in 25 per cent of 281 patients who did not show a definite clinical improvement on routine treatment the use of intraspinal therapy produced clinical arrest. Tryparsamide under similar circumstances produced decided clinical improvement in 28 per cent, and malaria therapy was likewise successful in 20.5 per cent. When a study was made of the influence of the various schemes of treatment on clinical progression it was found that in a group of tabetics who were receiving various types of treatment clinical progressions appeared in 30 per cent; when intraspinal therapy was added the incidence of clinical progressions dropped to 8 per cent. Malaria decreased progressions from 16 per cent to 11 per cent and tryparsamide did not exert any material influence in this regard.

Clinical progressions were noted in 14 per cent (139) of the entire group of 908 tabetics. Advanced forms of tabes dorsalis, general paralysis, taboparesis and vascular neurosyphilis were the most common types of progression noted. In those who had the Group III type of spinal fluid the majority of the clinical

progressions were to general paralysis while in most of those who had the Group II type of fluid advanced signs of tabes dorsalis developed. In 15 per cent of the patients who had a negative spinal fluid at the time the diagnosis of tabes was made clinical progressions occurred.

In this material the clinical response was usually preceded by the serologic reversal however the proportion of cases which obtain neither a clinical nor serologic response increases with the severity of involvement of the spinal fluid. Although clinical arrest was accompanied by serologic reversal in 70 per cent it is to be noted that clinical progressions may also appear in the presence of spinal fluid negativity In 13 per cent who did not obtain serologic reversal clinical arrest was noted hence spinal fluid findings in tabes dorsalis do not always parallel the clinical outcome of the case

Symptomatology —The outstanding observations made on the influence of the various treatment methods on the symptoms of tabes may be briefly summarized as follows In 13 per cent of the patients with optic atrophy the vision was improved and in 36 per cent the progressive loss of vision was stopped. Malaria therapy was more successful than the other therapeutic measures in controlling optic atrophy after the patients had been given moderate amounts of chemotherapy

Charcot's joints were improved in 7 per cent and arrest of the process was noted in 56 per cent none of the systems of treatment demonstrated any marked superiority in this manifestation of tabes. Twenty per cent of the patients with Charcot's joints had negative blood and spinal fluid reactions.

Trophic ulcers were completely healed in 47 per cent, with no outstanding benefit from any therapeutic measure.

Ataxia disappeared in 15 per cent of the cases and in 41 per cent it was materially improved, and although the results were about the same from the four methods of treatment there were fewer cases that showed an advance in the ataxia following intraspinal therapy

The neuritic pains were the most frequent symptoms of tabes and they were completely overcome in 31 per cent of the cases, while in 35 per cent the severity and frequency of the pains were lessened. Routine treatment alone had a higher percentage of successful results than did any of the supplemental measures in that 32 per cent of the patients had a complete disappearance of the pains following this type of treatment. Malaria therapy was the least successful in the control of this symptom due no doubt to the fact that it was employed in the cases in which the other methods had given no relief

Gastric crises disappeared following treatment in 44 per cent and were less severe in 25 per cent. Routine treatment was again the most successful method of treatment.

Incontinence disappeared in 24 per cent, while in 38 per cent the complaint was improved. Malaria therapy was most successful in the control of this complication.

Diplopia was the most responsive symptom to treatment, as it disappeared in 83 per cent of the cases and in the majority of the cases from routine treatment.

It will not be possible to estimate accurately the value of any specific or nonspecific therapeutic program for tabes dorsalis until the incidence of cases in which the symptoms of the disease disappear spontaneously as well as those that progress to the end point A study of the influence of treatment on the objective signs of the disease was not attempted.

Nutritional deficiency and [illegible] —The clinical and experimental [illegible] suggesting [illegible] of tabes dorsalis

may lie in a combination of nutritional deficiency and neurosyphilis is summed up by Moore and Woods. So far however this hypothesis has not led to any practical therapeutic suggestions except for the now demonstrated value of thiamin chloride (vitamin B_1) in the treatment of tabetic lightning pains. Too little is as yet known to explain the relief which thiamin affords in this respect and there is no knowledge as yet as to the nature of the deficiency in tabes if one exists or as to whether thiamin or any other vitamin component will be beneficial for other symptoms of the disease The field is a fruitful one for study

The Treatment of Taboparesis

This condition should be managed at the start precisely as if the entire picture were paretic, the tabetic element being temporarily neglected. Unless properly treated, the patient will probably die of paresis before he is incapacitated by tabes Fever therapy should be given at once the possible risk from a cord bladder accepted. If a satisfactory remission develops from the standpoint of paresis the symptoms of tabes which in commode the patient may be dealt with later

The Treatment of Paresis

Untreated paresis is always fatal, death being preceded by a period of mental incapacity necessitating hospital care. This fact justifies the acceptance of the risks of drastic treatment inadvisable in less serious forms of neurosyphilis. It is to be emphasized however that the diagnosis of paresis is permissible only on the grounds of psychiatric and neurologic examination it cannot be made on serologic grounds alone. Standard treatment with the arsphenamines or mapharsen and heavy metals is of little or no avail and should not be used even as a temporizing measure. Fever therapy should be employed as soon as the diagnosis is made or if this is impossible, tryparsamide, the only chemotherapeutic agent of demonstrated value should be given until arrangements for fever can be made.

The three most important considerations which may interfere with the immediate use of fever therapy are its unavailability its cost, or the patient s physical condition The first and second of these objections are met by the fact that in nearly every State in the Union some medical center has facilities for administering fever therapy under such varying conditions of cost that all patients whether free part pay or pay can be accommodated. It is obligatory upon the physician who makes the diag nosis to refer his patient to such a medical center if he himself lacks the facilities or experience for treatment.

In certain patients especially those whose illness has been accompanied by marked loss of weight, leaving the patient in an undernourished per haps mildly anemic condition the physician sometimes wishes to defer fever therapy until tonic treatment has improved the general physical condition. Though this may occasionally be advisable, it is in most cases dangerous temporizing. While the patient is being treated with rest, forced feeding, iron and mild antisyphilitic treatment irreparable de-

struction of brain parenchyma may be occurring Desperate situations usually justify desperate risks It is surprising how well fever therapy is tolerated even by patients in poor condition often with the result that at its conclusion there is prompt improvement in physical as well as mental status

Disclosure of the diagnosis to the patient and his family — It is unwise to tell a paretic patient that he has paresis to say that he has neurosyphilis is all that is necessary There is risk that either before or after treatment, and especially if recovery occurs the patient s too detailed knowledge of his own illness will add a reactive depression to his other mental difficulties. On the other hand no matter how little mental deterioration may be apparent before treatment, and no matter how much the patient may object to disclosure of the fact that he has syphilis it is essential to inform a responsible member of the family of the diagnosis The course of the disease is subject to unpredictable variations a patient who is seemingly nearly normal may lose his judgment so rapidly as to involve an unsuspecting family in serious social or financial difficulty or he may even suddenly become a suicidal or homocidal maniac It is *essential also pending the outcome of treatment, to remove the patient* from the control of his affairs which should be placed in the hands of a responsible relative. This may sometimes be accomplished unobtrusively and without difficulty or it may be necessary to resort to legal methods

Whether it is better to discuss the situation with the marital partner or with another relative depends on individual circumstances The gravity of the situation should not be minimized the methods of treatment and their potential risk must be thoroughly explained Social and financial problems must be frankly discussed It is well to enquire as to whether the patient s life insurance if any contains a permanent disability clause Since even under the most favorable circumstances the period of disability will be in excess of 3 months this safeguard often included in insurance policies without the knowledge of the beneficiary may ease the financial strain.

Hospitalization —It is of course essential to admit the patient to a hospital for fever therapy Whether treatment can be carried out successfully in the medical service of a general hospital, or whether confinement in a psychiatric hospital is necessary depends entirely on the patient s mental status. If he is so disturbed that he cannot be easily kept in bed if he is inclined to be so noisy as to annoy other patients if he is so depressed as to be suicidal a psychiatric hospital is obligatory In any case and even if the patient is apparently so docile and cooperative as to permit his management in a general hospital permission for commitment if emergency requires it should be obtained from a responsible relative.

The immediate results of fever therapy in paresis —During the actual febrile paroxysms a frank delirious state may be added to the patient s other mental abnormalities. In addition psychiatric symptoms already present may become much worse The patient becomes more excited depressed or expansive, as the case may be the speech becomes even more dysarthric convulsions if they have previously occurred are

likely to recur during the fever * In many instances, however there is definite mental improvement during the course of the fever, and within a week or two after its completion there may be an almost complete transformation of personality From the physical standpoint there is usually a prompt gain in weight, beginning a week or two after the termination of fever There is a rough correlation between gain in weight and its extent with the probability of psychiatric improvement. If the patient fails to gain during the first month or two, mental improvement is less likely than when he attains or even slightly exceeds his average normal weight

The classification of ultimate results of fever therapy.—The statements made in this section apply almost entirely to the results of malaria therapy While the character of results obtainable from other forms of fever therapy is identical, it is already known that from certain forms of treatment (relapsing fever rat-bite fever foreign protein therapy) the frequency of a favorable outcome is not as great nor the average duration of remissions as long as with malaria. The results from other physical methods (diathermy radiothermy etc.) will be discussed separately

Though improvement in the mental status may occur actually during the course of fever it may also be delayed for several weeks or months. World wide experience has demonstrated however that *if a change for the better does not appear within 6 months it probably will not occur at all*. If malaria and the appropriate after-treatment have been unsuccessful in effecting any betterment during this period of time, the chance of obtaining it from any form of treatment, even including a second trial of fever therapy is so small as to make further therapeutic efforts unjustifiable unless the family's finances are almost unlimited.

Somatic improvement in paresis.—Following malaria there is frequently prompt disappearance of the speech defect and of the facial and generalized tremulousness. Other neurologic abnormalities such as pupillary and reflex changes are usually unaltered. Some observers have reported the return to normal of Argyll-Robertson pupils, and we ourselves have observed this phenomenon but it is rare. General physical improvement is manifest by a sense of well being and by prompt gain in weight.

The psychiatric results of treatment.—Since the outcome of treatment in paresis is measured more largely in the psychiatric than in the physical field a different terminology from that in use in other forms of neurosyphilis is required. The treated paretic patient will ultimately fall, speaking generally into one of five categories, as follows

1 Complete remission This indicates that all psychiatric abnormalities such as defects in memory judgment, calculation speech and writing, all disturbances of mood delusions etc. disappear the patient regains insight into his previously abnormal mental condition, his physical condition improves and he is able to resume his usual occupation and his place in society with his former efficiency Some patients whose degree of im-

* In a paretic patient known to have severe grand or petit mal convulsive seizures, an anti-convulsant drug (phenobarbital, dilantin) should be given before, during, and after fever therapy

provement warrants their inclusion in this group may nevertheless retain slight residual mental defects chiefly in retention calculation or memory When this favorable outcome occurs, it is likely in about 85 per cent of the fortunate patients, to be maintained over a period of many years (in some patients now as long as 20 years) In about 15 per cent, subsequent relapse will occur usually within the first 5 years of the remission.

2 Incomplete remission In this group fall individuals whose psychiatric improvement while sufficient to permit the patient to engage in some useful occupation either in or outside the hospital is inadequate to permit resumption of his usual occupation or social activities Permanent residual defects remain, usually including complete lack of insight. Physical improvement is also the rule. Further evidence of progress of the paretic process is often lacking the patient remains at his subnormal mental level over long periods of time. Subsequent relapse is however more frequent than in those patients attaining more complete remissions.

3 Incomplete remission more obvious in the physical than in the psychiatric sphere There is little or no mental improvement, though the patient s physical status undergoes a distinct change for the better, progress of the disease apparently ceases and the unfortunate patient may remain for years in this state of affairs unsatisfactory alike from the standpoints of patient, his family and physician. Included in this category are those interesting patients noted by Gerstmann and others, whose psychosis changes, following fever therapy from the usual paretic to a schizophrenic (paranoid-hallucinatory) type This is the worst of all possible outcomes for the patient and his family He remains so ill mentally as to necessitate his confinement in an institution but improves so much physically that he may live for years.

4 Unimprovement, physical or mental Fever therapy appears to be without effect the patient continues a rapid or gradual downhill physical and mental course and dies in about the same length of time as if nothing had been done.

5 Death during or shortly after malaria, as a direct or indirect result of the treatment itself

Factors affecting the outcome of malaria therapy —Two elements of great importance enter into the estimate of the probable effect of fever therapy These are, first the duration of paretic symptoms second, the type of paresis. It is probable that both these factors are intimately related to the extent of inflammatory as compared with degenerative change This is certainly true of the element of duration of symptoms and perhaps, though there is less definite correlation between pathologic findings and type of clinical psychosis, true also of this factor as well.

The probability of a complete remission stands in direct relationship to the duration of paretic symptoms before treatment. The earlier treatment is given the more likelihood of a favorable outcome Owing to the insidious nature of the onset in many patients and to the manner of reporting results in the literature definite percentage figures covering this all important point were not available when the first edition of this book

was written. Now, however, the deficiency has been supplied by careful studies of 300 cases by Pfeifer and von Rohden and of 205 cases by Freeman and his associates. Each of these groups of workers estimated the outcome of malarial therapy in paresis as related to the duration of paretic symptoms at the time fever was given. The series do not wholly parallel because different time intervals were employed but the data are presented as curves in Fig 77 If malaria could be given within the first 2 months of symptoms Pfeifer and von Rohden obtained complete re-

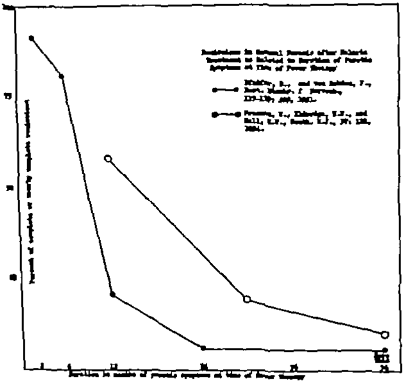


FIG. 77

missions in nearly 90 per cent within the first 6 months in about 80 per cent but when symptoms had been present for 6–12 months only about 20 per cent were so fortunate. Freeman and his co-workers did not attempt such fine time divisions but obtained about 60 per cent remissions in patients ill with paresis less than one year Both groups agree that when paretic symptoms have been present 2 years or longer before fever therapy is given the probability of complete remission drops off to 10–20 per cent or less.

This is a convincing demonstration of what is after all no more than is to be anticipated. Treatment of any nature cannot be expected to revivify dead brain cells. The longer the paretic process exists before treatment,

the more actual destruction of brain parenchyma occurs and the less likely is restoration of function. This relationship speaks urgently for the early recognition of paresis and is a factor largely responsible for the extension of malaria therapy to those neurosyphilitic patients who though not clinically paretic, may be expected possibly to become so in the future.

The prognosis is distinctly better in patients with manic, manic-depressive and expansive psychoses than with other forms. Next in order come respectively patients with depressive, simple dementing, and paranoid psychoses. So-called "galloping" paresis has a poor outlook, as does also juvenile paresis, the latter probably because the onset is usually so insidious that irreparable damage is done before the diagnosis is made. The variation in outlook with these different types of psychoses is probably also related to the degree of degeneration at the start of treatment since in the manic and expansive forms, the onset is relatively acute and the diagnosis made early.

Not infrequently in apparently uncomplicated paresis the institution of malaria therapy may be followed by urinary retention, either partial or complete. Cystometric studies by Lewis and Langworthy of patients *in whom this has occurred have disclosed previously unsuspected involvement* of the posterior columns. This is apparently a much more frequent complication of paresis than has been generally suspected. If the retention is noted before distension of the bladder is marked, the administration of mecholyl, 10 mgms. 4–6 times daily, with careful supervision of the patient's habits of voiding will usually restore bladder function. If these measures fail, a two-way indwelling catheter should be installed and the bladder irrigated with a mild antiseptic solution. This should be done under the direction of a competent urologist, not only because the too rapid reduction of pressure may be harmful but because of the ever present danger of ascending urinary infection. Complete recovery of bladder function after the termination of malaria is the rule.

Paresis in elderly patients (over the age of 60) has a relatively poor prognosis, probably because the patient is less well able to stand the strain of fever therapy. Such other factors as race, sex, duration of syphilitic infection, or type and amount of antisyphilitic treatment prior to the appearance of paretic symptoms appear to have no influence on the outcome of treatment.

The general results of malaria in paresis.—The introduction of malaria therapy was followed by its application in psychiatric hospitals all over the world to paretic patients of all types, early and far advanced, of all degrees of mental deterioration, and largely without regard to physical condition. Even with such an unpromising clinical material as this, and although the death rate from treatment was high, the incidence of complete remissions was much better than from any previous form of treatment. Most of the published results are from psychiatric hospitals and deal with unselected series of patients. In a clinical material such as our own, where the diagnosis of paresis can often be made very early in its course, and where the risks of treatment can be minimized by the careful selection of patients, the proportion of remissions rises and the

TABLE 92

THE PROBABLE OUTCOME OF MALARIA THERAPY IN PARESIS

	Estimated percentage probability of				
	Complete remission	Incomplete remission, but able to work	Incomplete remission, permanent hospitalization required	Unimproved	Death during or shortly after treatment
Unselected clinical material (including all types, early and advanced)	25	20	25	20	10
Selected clinical material (mostly early cases, in good physical condition) †	35	28	25	10	2

Based on more than 12,000 reported cases.

† Based on about 1,000 patients treated in our own clinic.

death rate from treatment falls. In Table 92 we have indicated the probable percentage outcome of treatment in unselected patients, based on various summaries of the reports in the literature, as compared with a similar estimate in a selected series mostly of early paresis.

The necessity for the duration and the desirable type of antisyphilitic treatment following the fever therapy of paresis — The earlier patients treated with malaria were given no after treatment. It shortly became apparent, however that after treatment was desirable for three reasons —it increased the probability of complete remission it guarded against paretic relapse and it prevented the further progress of syphilitic processes elsewhere in the body than the brain. The advantage gained in the first two of these respects is not directly presentable in statistical form though it is probable that the likelihood of complete remission is increased by 2–8 per cent, and of subsequent paretic relapse diminished by an equal proportion as a result of energetic after-treatment. Even if these two considerations were not operative, however pathologic studies of malaria-treated patients have supplied adequate reason for such treatment. Fever is without apparent permanent effect on syphilitic lesions in other tissues than the nervous system, and such lesions especially in the aorta (and liver?) are commonly associated with paresis Moreover the pathologic process in the brain may not be entirely eliminated but altered in character from that of parenchymatous to mesoblastic neurosyphilis (Straussler and Koskinas) the latter far more easily susceptible to chemotherapeutic measures than the former And finally in malaria treated patients the mechanism of resistance to infection may be so enhanced or altered as to produce an allergic state, with the subsequent development of gummatous lesions.

It is almost universal practice as soon as the malaria is completed and a few days of recuperation allowed to give a short course of small doses of neoarsphenamine or mapharsen. This is partly for antisyphilitic effect, but more largely because of its general tonic effect on the patient and its supplementary action to quinine on the malarial infection. Treatments may be given at 5–7 day intervals in a dosage of 0.3–0 6 gm. of neoarsphenamine 0 040–0 060 gm. mapharsen.

In our own clinics it is customary as soon as this course of neoarsphenamine is completed to institute the immediate use of that arsenical drug known to be of value in paresis tryparsamide (unless of course there is an already existing optic atrophy) This drug is given in courses of 12–16 weekly injections of 3 0 gms each the interval between such courses being occupied by courses of 8–12 injections of 0.2 gm. each bismuth subsalicylate. This type of treatment is given continuously without rest in tervals In many cases we have recently employed much longer tryparsamide courses 25–50 or more consecutive injections combining occasional simultaneous courses of bismuth.

If there is no evidence of clinical improvement at the end of 6 months of *this form of treatment, serious consideration is given to the question of* desirability of further treatment. There is little chance of further benefit under these circumstances and, in order to conserve the family's financial resources for the sake of wife or children, it may be better to abandon fur ther therapeutic efforts and to arrange for the least expensive form of permanent hospitalization for the patient.

If on the other hand, improvement has occurred treatment with al ternating courses of tryparsamide and bismuth should be continued for an absolute minimum of 2½–3 years dating from completion of malaria. This type of post-fever treatment is now current practice not only in our own clinics but in most other American clinics as well. Abroad, where tryparsamide has not yet attained the same vogue as in this country similar though less prolonged after treatment is carried on with alternating courses of an arsphenamine and a heavy metal.

Comparative results of tertian and quartan malaria —The results of treatment with quartan malaria in paresis first used by Kirschbaum in 1928 are available in only a few hundred cases in contrast to the many thousands treated with the tertian strain. The data summed up in recent articles by Fong and (from our own clinic) Kroll are difficult to analyze accurately There are variations in the method of reporting and at least in this country the quartan strain has been used almost wholly in Negroes in whom the paretic disease is often of longer duration when treatment is given than in white patients As nearly as can be determined however complete remissions are obtained in only about 10–15 per cent of quartan treated patients and reasonably satisfactory incomplete remissions in about 30 per cent a total of about 45 per cent improved These figures should be compared with the usual average of 35 per cent complete and 30 per cent incomplete remissions (65 per cent improvement) after tertian malaria and indicate that quartan is distinctly if only slightly less satisfactory

The relative value of various fever inducing agents in the therapy of paresis —Opinions concerning the value of the different methods for producing fever in the treatment of paresis vary considerably In most European clinics and in several of the large clinics in this country, including the Johns Hopkins clinic it is felt that the results following malaria are superior in terms of the incidence of complete remissions and their prolonged maintenance to those from other forms of artificially induced fever It is certainly true that malaria is more effective than relapsing or rat-bite fever or foreign protein shock.

The various mechanical methods for the induction of fever i e. diathermy fever cabinets, fever blankets short-wave radio and radiant heat have not been individually evaluated. According to Bishop Lehman and Warren there is little to choose between radiant energy diathermy and radiothermy The enthusiasm of Neymann and his collaborators for electropyrexia, i.e. fever induced by high frequency currents is apparently based on their desire to propagandize this type of fever therapy and is not shared by other observers who can neither confirm their results nor find reason to condemn malaria so heartily Freeman Fong and Rosenberg, in summarizing the literature as to diathermy present a table which shows on analysis that while some enthusiasts report 83 per cent remissions with only 6 per cent deaths, others, dealing with equally large numbers of patients, could obtain only 12 per cent remissions and 15 per cent deaths. In 50 patients treated by Freeman and his associates there were no remissions and only 10 patients could be regarded as improved. Furthermore pathologic studies of the brains of 7 of their patients dying after treatment, showed little or no evidence of improvement in striking contrast to the findings in malaria-treated patients. This explains the observations of Epstein, Solomon and Kopp, who found that although fever produced by diathermy was of some value in the treatment of paresis, the results were much less satisfactory than those following malaria.

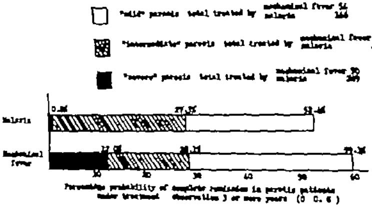


FIG. 78

The only extensive comparison of the results of malaria and mechanical fever in the treatment of paresis is furnished by the C.C.G. (Fig. 78)

In patients with "mild" paresis, i.e. those with transitory mental symptoms only and without deterioration, and those with "intermediate" paresis i.e. moderate deterioration manic excitement or depression the results with both types of fever were practically the same However in advanced paresis complete remissions occurred in only 0.8 per cent of *patients following malaria in contrast to 12.0 per cent following fever induced mechanically* Unfortunately it is impossible from this study to evaluate individually the various mechanical types of fever therapy which were employed and particularly unfortunately there are no comparative data on the all important point (cf above Fig. 77) of the duration of paretic symptoms at the time fever therapy of whatever type was given.

While the argument as to the relative merits of malaria versus mechanical fever is far from settled even by the elaborate C C G study it *seems clear that mechanical fever does have some merit in the treatment of paresis* While our own preference is still for malaria, tertian or quartan we believe that the physician should employ that method with which he is most familiar, and which is most readily available.

CHOICE OF METHOD OF FEVER THERAPY

Use that method which is
(a) readily available, and
(b) with which you are most familiar

FIG 79

The social management of the treated paretic —The problem *presented by the paretic patient who does not improve is relatively minor* He must usually be subjected to continued hospital restraint, with the management of his affairs in other hands than his own. When improvement occurs grave problems not infrequently arise. How soon shall the patient be allowed to return to his occupation? Each case must be decided on its merits. In general it may be said that where the occupation involves the safety or the lives of others as for example with locomotive engineers or physicians a full year of maintained complete remission *should be insisted upon before a return to work is allowed If there is no* question of others, physical labor may be permitted as soon as it is obvious that the remission is complete occupations involving mental activity should not be resumed until the remission has been maintained for 6 months In any case the family and if possible a responsible employer or business or professional associate should be warned of the possibility of relapse.

The resumption of marital relationships is sometimes a troublesome question Its decision, it seems to us is based largely on the question of the avoidance of future pregnancies. This is important not so much because of the possibility of transmission of infection to the child (which de-

pends on whether the wife is already infected) as on the financial issues involved by the uncertain outlook for the future. If husband and wife are agreed that reliable contraceptive measures will be used and are able to surmount the mental hazards involved restrictions may be lifted.

The management of paretic relapses—As we have already stated, relapse may be expected in about 15 per cent of the patients fortunate enough to obtain complete remissions. It may occur either during the period of treatment or later usually between the first and fifth year of the remission, rarely later Its appearance should be the signal for renewed therapeutic effort. Fever therapy is again the method of choice, tertian malaria if possible (see p 374) but, if not, some other method and with chemotherapeutic after-treatment as for the original attack. The prognosis for recovery from a relapse is distinctly poorer than from the original attack, but it may occur We have seen one patient who relapsed five times within a 12 year period. After the original attack he developed a complete remission lasting 2 years after each of the next three relapses, incomplete remissions, ranging in duration from a few months to 4 years the fifth and last relapse has ended in death. In the interim, however he had been kept alive and employed in a simple useful occupation, to the delight of his family

The Serologic Control of Treatment in Neurosyphilis

Serologic tests of the blood—As with other types of syphilitic infection, the response of the serologic tests of the blood to treatment is an accurate measure of the efficiency of treatment in early but not in late neurosyphilis. In early asymptomatic neurosyphilis and early acute syphilitic meningitis the serologic tests may usually be reversed to and maintained as negative, and together with the response of the abnormal spinal fluid to treatment, this phenomenon may and should be used as a guide to the duration of treatment. A safe rule in early neurosyphilis is identical with that for early syphilis in general (Chapter XIII) to administer continuous treatment until serologic tests of the blood and cerebrospinal fluid have become normal and have remained so for one year In the majority of cases this can be accomplished.

In late neurosyphilis on the contrary the serologic tests of the blood are of little or no value as a treatment guide. Seroresistance is common, and this may be true even when the spinal fluid changes completely disappear As time goes on we personally pay less and less attention to the serologic response of the blood as affecting the duration or termination of treatment and frequently we tell a patient that if he improves clinically and remains well, and if his spinal fluid shows a change for the better the state of the serologic test of his blood is of little practical importance. Actually however it seems to us probable that in many such patients the cause of seroresistance if this phenomenon depends on the presence of foci of syphilitic inflammatory tissue lies without the nervous system and that its real significance is that during the periodic re-examinations obligatory after the completion of treatment, evidences of progress in other structures than the nervous system (especially the cardiovascular

apparatus) should be carefully searched for It is never *justifiable, how* ever to prolong treatment indefinitely in the neurosyphilitic patient who otherwise is doing well, merely because the serologic tests of his blood remain positive.

The spinal fluid abnormalities —The important phase of the serologic control of treatment in neurosyphilis lies in its effect on the spinal fluid abnormalities Even this is more useful for measuring the immediate than the ultimate effect of treatment. As we have repeatedly stressed in preceding sections the treatment of neurosyphilis is largely a system of trial and error Almost any plan of treatment if intensive and prolonged enough will produce immediate symptomatic improvement in most cases (excepting tabes and paresis) Almost any plan of treatment also will effect a rapid decrease of excess cells and protein content the real test of efficiency lies in a reduction of Wassermann positivity or a change toward normal in the colloidal curves, or both. It is generally conceded that it is desirable to reduce the spinal fluid to normal and to maintain it so

In order then to determine the desirability of continuing a given treat ment scheme it is desirable to decide not only on the basis of symptomatic, but also on that of serologic, improvement. Spinal fluid examina tions should be done at intervals of six months during treatment and if possible repeat tests should be carried out in the same laboratory so that *an adequate basis of comparison is furnished.* Reduction in cell count or in protein content may in general be disregarded this occurs so promptly even with inefficient treatment as to be of little value in measuring treatment effect. Assuming that symptomatic improvement has occurred, and if there is reduction in the Wassermann titre (e.g. a

TABLE 93

SEROLOGIC RESULTS (SPINAL FLUID) IN VARIOUS TYPES OF NEUROSYPHILIS

Type of neurosyphilis	Estimated percentage probability of attaining permanent spinal fluid normality by means of			
	Standard intensified treatment (arsphenamines and heavy metals)	Subdural treatment	Tryparsamide	Fever therapy
Early meningeal (including asymptomatic)	80–90	80–90	80–90	80–90
Late diffuse meningovascular	50–60	50–60	60–70	70–80
Tabes	40–60	70†	60†	60–80†
Paresis	0– 2	0– 5	25–30	50–60

These estimates are drawn from our own experience and from various sources in the literature.

Of these, nearly a half have normal fluids before treatment.

† Including only patients with abnormal fluids before treatment.

test originally positive with 0.1 cc. later requires 0 4 cc. to produce fixation), the original treatment plan may be continued. If on the contrary the Wassermann remains unchanged it is wise to adopt a more drastic treatment method, proceeding, except where special indications as outlined above arise in the direction of standard routine→intensified routine→tryparsamide→fever therapy Each new procedure adopted should be given a trial of at least 6 months before abandoning it as without serologic effect.

Generally speaking, the earlier the involvement of the nervous system, the easier to secure and maintain serologic negativity in the spinal fluid. The approximate extent to which this may be secured in various types of neurosyphilis and by various treatment methods appears in Table 93 With almost any method of treatment, the same proportion of good serologic results may be obtained in early meningeal neurosyphilis but in individual cases a spinal fluid refractory to one method of treatment may be reversed to normal by another Almost the same is true, though in lower proportions, in late diffuse meningovascular neurosyphilis, though here tryparsamide and fever therapy are respectively more influential than standard treatment with or without the addition of subdural therapy In tabes, standard intensified treatment is of comparatively small effect the apparent high incidence of serologic reversal from this form of treatment is due to the inclusion within the group of a large number of patients whose fluids were normal before treatment, and in whom more intensive methods seemed undesirable or unnecessary

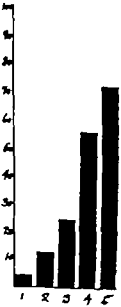


FIG. 80 — The percentage of negative spinal fluids observed in large malaria-treated [illegible] studied at yearly intervals after the [illegible] tion of malaria

Considering only those tabetics with abnormal fluids before [illegible] subdural therapy effects twice as many serologic reversals as [illegible] treatment and seems, in this respect, better than tryparsamide and [illegible] as good as fever therapy In paresis, there is little or no [illegible] from the arsphenamines and heavy metals, with or without [illegible] treatment a fair number of reversals are secured by tryparsamide [illegible] and a much higher proportion by fever therapy

There is a curious difference in the serologic effect of [illegible] compared with all other methods of treatment. From the [illegible] of serologic improvement, if they occur at all, appear [illegible] apparently as a direct result of treatment. From the [illegible] improvement is the exception not the rule if it occurs at all [illegible] delayed for at least 18 months after the completion of [illegible] appears to be progressive over a period of years. The [illegible] workers in this field has been identical. It is well [illegible] showing the percentage of malaria-treated paretics [illegible]

fluid becomes normal at varying intervals after treatment. Within the first year after malaria, only a very few patients achieve serologic negativity, and the proportions are only moderately increased during the second and third years. Four years after treatment, more than half of those still living have normal fluids and five years after nearly three-fourths have reached this point.* This phenomenon of delayed and progressive serologic effect from malaria occurs whether or not additional antisyphilitic treatment is given after the malaria is terminated. To a lesser extent, it apparently occurs also after other forms of fever therapy. The phenomenon is a potent argument in favor of the view that the effect of fever therapy in general and of malaria in particular depends in part on some other factor than its ability to destroy treponemes.

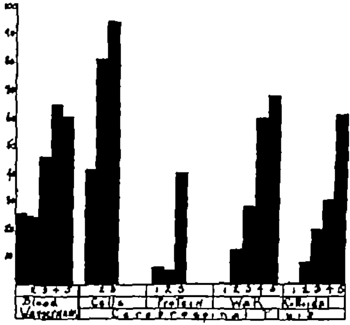


FIG. 81.—The percentage incidence of reversal to normal of blood Wassermann and of various spinal fluid abnormalities in malaria-treated paretics, studied at yearly intervals after the termination of malaria (after White)

The rate at which different tests of blood and spinal fluid in paretic patients is affected by malaria is variable. Within the first two years as shown in Fig. 81 the blood Wassermann is reversed to negative in about 25 per cent of patients by the end of the third year 45 per cent, by the fourth year 65 per cent with little subsequent change. As with other forms of treatment there is an early return of the cell count to normal in

* These data vary in different clinics with variation in the sensitivity of the serologic test employed. In our own clinic, which uses a delicate icebox complement fixation test, the proportion of negative fluids in treated neurosyphilitics, paretic or otherwise, whether or not treated with malaria and no matter at what interval after treatment, is lower than in many published reports.

TABLE 94

CORRELATION OF EXCELLENT CLINICAL RESULTS WITH NORMAL SPINAL FLUID SEROLOGY IN VARIOUS TYPES OF NEUROSYPHILIS (AFTER HOPKINS)

Type of neurosyphilis	Percentage of absolute correlation (i.e., percentage of patients with excellent clinical results who also were rendered serologically negative)
Early meningeal (including asymptomatic)	83
Late diffuse meningovascular	70
Tabes	40–54
Paresis	55

nearly all patients. Protein Wassermann and colloidal curves return more slowly to normal, the last named most slowly of all.

Correlation of clinical and serologic results.—Though prolonged serologic negativity is certainly desirable in neurosyphilis as in other forms of syphilis generally it is not an absolute criterion of clinical inactivity Even untreated patients are encountered in whom clinical progression occurs in the face of normal blood and spinal fluid findings. This occurs usually in tabes or in more or less purely vascular neurosyphilis Likewise there are numerous patients, especially tabetics and paretics in whom a return to serologic normality is unaccompanied by symptomatic improvement, or in whom *further evidences of progress appear after* treatment has apparently accomplished both clinical and serologic arrest, e.g., the development of a Charcot joint in a well-treated tabetic, years after the cessation of treatment.

On the other hand, there is a still larger number of patients in whom the clinical result is excellent with complete symptomatic relief and permanent cessation of progress but in whom serologic normality of the spinal fluid is apparently unobtainable with any treatment method now at our command. This group of patients is considered in detail in subsequent paragraphs.

In general clinical and serologic improvement go hand in hand in early meningeal and late meningovascular neurosyphilis while there are wide variations between the two in tabes and paresis. In Table 94 is shown Hopkins' correlation of these two factors in the Johns Hopkins material. When the inflammatory lesion in the nervous system is predominant (early meningeal or late meningovascular) from 70–80 per cent of all patients who obtain an excellent clinical result from treatment are also rendered serologically negative. When the lesion is chiefly degenerative (tabes and paresis) only about half the patients who do well clinically are as fortunate from the serologic standpoint.

The duration of treatment as affected by serologic outcome.—The physician treating neurosyphilis has three things to guide him as to

In such patients, treatment may produce an apparent provocative effect in the spinal fluid (Solomon and Klauder) definite abnormalities, especially a positive Wassermann, may appear in a previously normal fluid as the apparent direct result of treatment.

the total duration of treatment—his patient's clinical status, his knowledge of the ultimate outcome in a large series of similar patients treated by diverse methods and over varying periods of time and his patient's serologic response. Of these, the two former are more important than the latter in determining the duration of treatment. It is possible to say arbitrarily on the basis of the experience of many observers who have studied large groups of patients, that to achieve clinical arrest (not merely symptomatic improvement) in any type of neurosyphilis early or late, prolonged treatment is essential In no case should the duration of treatment be less than 2–3 years. If at the end of this time the patient's serologic response is such as to indicate that negativity of the spinal fluid (disregarding the blood serologic response almost entirely) may be obtained it is unquestionably desirable to continue until this point is reached and if it is reached for 6–12 months thereafter Should the spinal fluid show very little improvement, treatment should never be stopped until fever therapy has been employed, no matter what the character or duration of previous treatment. If during 3 years of treatment which has at some time included fever therapy the spinal fluid abnormalities reach a stationary level short of complete normality treatment may be stopped provided rigid post-treatment control is carried out.

The relation of persistently abnormal spinal fluids to ultimate prognosis in well treated neurosyphilitic patients —Every physician who treats neurosyphilis is familiar with and discouraged by the problem presented by the patient with persistent abnormalities in the cerebrospinal fluid. This phenomenon occurs in patients with varied types of neurosyphilitic involvement—paresis, tabes diffuse meningovascular lesions asymptomatic neurosyphilis. What is the significance of this situation for the patient's future? Does it mean that he is in constant danger of relapse or further progression of neurosyphilis, to avoid which treatment "for insurance must be prolonged for many years or even for a lifetime? Or on the contrary does it have the same relative insignificance as seroresistance of the blood in the average patient with well-treated latent syphilis? The relative lack of parallelism between serologic and clinical improvement in paretic patients treated with malaria, the fact that a complete and well-maintained remission may occur in such a patient in face of complete absence of serologic improvement suggests that the latter explanation might be the correct one.

In order to obtain some information about it Goodman and Moore surveyed the Johns Hopkins material, selecting patients on the basis of three conditions (1) that as a result of prolonged treatment, there had been marked improvement or complete relief from the symptoms of neurosyphilis (2) that in spite of prolonged treatment, spinal fluid abnormalities were persistent up to the point at which treatment was stopped (3) that after the conclusion of treatment the patient was followed with repeated neurologic and serologic examinations for a minimum period of 2 years Two hundred and twelve patients were available for study the results of which are presented in Tables 95 and 96 Of the 95 patients in whom the reaction of the spinal fluid remained positive 21 or

TABLE 96

NATURE OF RELAPSE OR PROGRESSION IN 212 PATIENTS WITH NEUROSYPHILIS
(From Goodman and Moore)

Type of Neurosyphilis	Persistently Positive Reaction of Cerebrospinal Fluid			Reversal of Reaction of Cerebrospinal Fluid		
	No of Patients	No. of Patients with Relapses	Type of Relapse or Progression	No. of Patients	No. of Patients with Relapses	Type of Relapse or Progression
Dementia paralytica	26 (14)	10 (1)	6 (1) relapse or progression of dementia paralytica 1 cerebral hemorrhage (?syphilitic) 1 formication of the face 1 hemiplegia 1 optic atrophy	11 (6)	0	
Tabes	16 (2)	4 (0)	1 locomotor ataxia worse 1 general progression 1 gastric crises worse 1 vesical symptoms worse	20 (3)	6 (1)	1 bilateral Charcot hip 1 ataxia worse 1 Charcot knee 2 (1) increased lightning pains 1 Charcot joint worse
Diffuse meningovascular	28 (4)	2 (0)	1 involvement of eighth nerve 1 dementia paralytica	28 (1)	1	1 Parkinson syndrome (?syphilitic)
Meningeal	9	2	2 dementia paralytica	25	1	1 optic atrophy
Asymptomatic	16 (2)	3 (0)	2 dementia paralytica 1 hemiplegia (?syphilitic)	33 (2)	0	
	95	21		117	8	

The figures in parentheses indicate the number of patients who received fever therapy

22.1 per cent, showed clinical evidence of progression. Of the 117 in whom the spinal fluid was reversed progression occurred in 8 or 6.8 per cent. Limited to patients treated for 2 or more years (Table 96), subsequent progression occurred in 12.5 per cent of the seroresistant group and in 4.8 per cent of those in whom reversal of the spinal fluid was secured.

TABLE 96

RELATIONSHIP OF AMOUNT OF TREATMENT TO CLINICAL PROGRESSION IN WASSERMANN FAST PATIENTS AND PATIENTS WITH REVERSED REACTIONS
(From Goodman and Moore)

Cerebrospinal fluid	Duration of Treatment	Number of Patients	Clinical Progression	
			Number of Patients	Per Cent
Persistently positive reaction (95 patients)	6 mos. to 2 yrs.	31	13	41 9
	Over 2 yrs.	64	8	12 5
Reversal of reaction after treatment (117 patients)	6 mos. to 2 yrs.	34	4	11 7
	Over 2 yrs.	83	4	4 8

As shown in Table 95 progression was more frequently encountered in patients with parenchymatous than in those with other types of neurosyphilis. Of the 10 patients who suffered relapse 6 showed progressive mental deterioration. All 10 had persistently positive spinal fluids. In the group of tabetics progression was as frequent among those who experienced reversal of the spinal fluid as among those whose fluids remained positive. In 2 of the former group relapse was evidenced by the development of Charcot joints a curious phenomenon which apparently occurs relatively frequently In the 9 patients with non parenchymatous neurosyphilis relapse was of the paretic type in 5 and in every instance was encountered among those whose fluids remained positive It is important that both in this group and in the group in which reversal of the spinal fluid occurred, clinical progression was less frequent in patients treated with malaria than in those who were not.

Of the patients with persistently positive spinal fluids after 2 years or more of treatment, 87.5 per cent were well for 2–16 years after the cessation of treatment.

These results are approximately as good from the clinical standpoint, as those observed in patients in whom treatment results in complete serologic reversal. Even though the number of patients is small certain conclusions are we believe permissible. With various forms of central nervous system syphilis persistently positive spinal fluid abnormalities do not indicate the certainty of subsequent progression or relapse provided the patient has been subjected to intensive prolonged and continuous treatment for a minimum period of 2–3 years provided this treatment has brought about symptomatic improvement or relief and especially provided malaria has been included in the treatment plan. On the contrary

such patients may be assured with reasonable certainty that the chances are at least 4 out of 5 that the good clinical result will be maintained over a considerable period of years and perhaps for an indefinite time. If relapse does occur it is likely to be manifest within the first 5 years after the cessation of treatment and is especially likely to be paretic in nature no matter what the type of the antecedent neurosyphilis.

What of progression or relapse outside the nervous system in these patients especially what of the probable liability to develop cardiovascular syphilis? Only one such example has been observed in a series of 44 patients studied by Moore, this a woman who has developed frank signs of uncomplicated syphilitic aortitis because of which treatment appropriate to cardiovascular rather than to neurosyphilis has now been resumed. The four deaths were from vascular accidents two cerebral, two coronary All these patients, however were over the age of 50 and in the absence of necropsy evidence, which unfortunately is lacking the rôle which a possible vascular syphilis may have played cannot be evaluated.

As a result of this study, we shall have much less hesitation in the future as to stopping treatment in the face of persistently abnormal spinal fluids.

The Post Treatment Management of Neurosyphilis

When the decision is reached to terminate treatment, either because the patient has achieved apparent clinical arrest and serologic normality or lacking the latter because an arbitrary amount of treatment has been given, the responsibility of the physician is by no means ended Subsequent relapse may occur demanding certainly if the relapse is clinical, or probably if it is serologic, the resumption of treatment. The patient's only real safeguard against progression or relapse is rigid post-treatment observation with frequently repeated physical and serologic re-examinations. The frequency with which these should be performed is important. Relapse is much more likely to occur within the first three to five years after the cessation of treatment than later For this period of time, therefore it is essential to review the situation at intervals of 6–12 months preferably the shorter period. Specific questions should be asked to bring out the possible return of symptoms complete physical and neurologic examination should be performed and the findings compared in detail with those of the original examination (remembering that progression may occur elsewhere than in the nervous system especially in the cardiovascular apparatus) and blood and spinal fluid serologic tests should be repeated. After the fifth year the interval between examinations may be lengthened to 12–18 months, the patient being instructed, of course, to report at once if new and puzzling symptoms appear In the case of paretics, the family rather than the patient should be warned to watch for signs of relapse.

Repeated examinations of this sort should be kept up for an indefinite period of time. Vigilance should never be relaxed it is often the price of the patient's continued good health. He may as a matter of fact regard these periodic examinations as a form of life insurance. Inasmuch as keen and critical judgment, covering a variety of complex examinations and

their interpretation, is often necessary to decide the question of relapse or progression and the advisability of resuming treatment, the syphilologist can often render a valuable consulting service to the less experienced practitioner in the management of this phase of neurosyphilis Certainly to be of maximum value repeated physical examinations should so far as possible be carried out by the same physician and repeated laboratory tests done in the same laboratory so as to provide an accurate basis of comparison with previous tests.

It is obvious that the reappearance of clinical symptoms or of progression in physical signs is a signal for the resumption of treatment no matter what the character or duration of previous treatment may have been. The type of treatment to be given for the relapse varies with the nature of the latter and may be decided in accordance with the principles outlined in this chapter

TABLE 97

THE PRINCIPLES OF TREATMENT OF NEUROSYPHILIS

1 Identify the type of neurosyphilis as accurately as possible by neurologic, psychiatric, and serologic study

2 Be familiar with the patient s general physical status—has he cardiovascular syphilis or other complicating disease?

3 Be familiar with the possibilities of and special indications for various treatment methods, including tryparsamide subdural and fever therapy

4. The aim of treatment is first, symptomatic relief second, clinical arrest, with freedom from subsequent progression or relapse third, serologic normality

5. Proceed by a system of trial and error and except for special indications, use least drastic methods first.

6. Gauge changes in treatment by clinical progress first, next by serologic progress.

7 Give each method of treatment a trial of at least six months, controlled by spinal fluid examination.

8. Treatment must be prolonged minimum under any circumstances 2–3 years.

9 If the spinal fluid changes are refractory to treatment, always advise fever therapy before probation.

10 Rigid post-treatment observation with frequently repeated physical and serologic re-examination

The question of serologic relapse is a more difficult one. What constitutes serologic relapse significant enough, in the absence of clinical evidence of progression to justify the resumption of treatment? The spinal fluid findings are the element of importance seroresistance or serologic recurrence in the blood is of small significance if any in this particular situation. If the spinal fluid has been rendered normal by treatment, the reappearance of pleocytosis or of Wassermann fixation in any amount of

fluid certainly justifies further treatment. Slight changes in protein content or in the colloidal curves which depend on protein may be disregarded. If on the other hand treatment has been stopped while the spinal fluid still retained abnormalities, serologic relapse must involve something more than fluctuations possibly due to technical variations in the laboratory If cell count and protein increase together to distinctly abnormal levels, or if there is a significant increase in the titre of Wassermann positivity treatment should be resumed regardless of clinical status.

Summary of Principles of Treatment of Neurosyphilis

We have attempted to summarize in condensed form, the major principles of the treatment of neurosyphilis (Table 97) which have been discussed in detail in this and the preceding two chapters. They apply with equal force to all types of neurosyphilis.

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CHAPTER XXV

THE TREATMENT OF LATE SYPHILIS COMPLICATED BY OTHER CONDITIONS

THE following discussion of the management of late syphilis complicated by other conditions is based almost entirely upon personal experience except as concerns the complications of tuberculosis diabetes and thyroid disease the literature is nearly devoid of worthwhile studies on this important subject. It is hardly necessary to repeat that before starting treatment in a patient with late syphilis of any type the physician should, by means of a full history complete physical examination and appropriate laboratory tests, satisfy himself as to the general physical status of his patient. The association of other diseases with syphilis may materially alter both the prognosis and the treatment procedures designed to improve it. Although it is manifestly impossible to consider all the complicated situations which may arise, we mention briefly the most frequent and important contingencies which we ourselves, as practical therapeutists have encountered.

Late syphilis and old age —This topic has already been briefly discussed in Chapters XVI and XXIV In an individual over the age of 60 the institution of treatment for syphilis and its type may properly depend on whether there are subjective or objective evidences of damage. If the disease is purely latent, accidentally discovered by means of routine serologic testing the physician is often justified not only in withholding treatment but even in failure to reveal the diagnosis. If mild constitutional symptoms but no definite objective physical alterations are present, the patient may often feel better after a month or two of very mild treatment, even so mild as 'mixed treatment (Chapter IX) by mouth. If on the contrary physical examination reveals the signs of cardiovascular or neurosyphilis, the patient must usually be treated in accordance with the principles of Chapters XVIII and XXIV For the inflammatory lesions of benign late, visceral or ocular syphilis treatment is of course obligatory but in most instances it may be mild (small doses, 0.3–0 45 gm. neoarsphenamine or 0 02–0.03 gm. mapharsen followed by mercury by inunction) and continued for only six months or even less. Prolonged punishing treatment to prevent relapse is unessential in elderly patients symptomatic relief is sufficient.

Late syphilis and malignancy —This subject has been discussed in Chapter XXIX The decision as to whether to treat the patient who has both syphilis and a malignant neoplasm depends first on whether the symptoms or lesions due to syphilis if any may be relieved by treatment and the patient made more comfortable second on the type operability and malignancy of the neoplasm, information which the physician can best gain by consultation with the surgeon and pathologist. Generally

speaking If the neoplasm is operable and the prognosis for its radical cure good the patient should be treated for syphilis in the same manner as a normal person if the neoplasm is inoperable, treatment for syphilis may usually be omitted as adding nothing but discomfort. However we have had the embarrassing experience of withholding antisyphilitic treatment from a patient with latent syphilis whose stomach was resected by Rienhoff for proved carcinoma only to see him return 9 years later apparently cured of the carcinoma but with an aortic aneurysm.

Syphilitic patients with precancerous lesions (leukoplakia, gumma) of the tongue or buccal mucosa should be energetically treated (Bloodgood) We are not convinced that in such cases malignant degeneration is prevented by antisyphilitic treatment alone local surgical or radiotherapy is also necessary The object of treatment is the prevention of local gummatous relapse which in its turn may assume neoplastic characteristics.

The association of syphilis with the lymphoblastomas has been mentioned in Chapter XXIX Treatment for syphilis should be continued until the diagnosis is clear and thereafter as long as the patient is progressing favorably under radiotherapy

Syphilis and tuberculosis—This subject has been discussed in some detail in Chapters XIV and XIX Tuberculosis of the adrenals (Addison's disease) is a definite contra-indication to the use of the arsphenamines (Chapter VII)

Late syphilis and acute infections—During the course of any of the acute infections treatment for syphilis should be discontinued until convalescence is well advanced. The chief exception to this rule is pneumonia.* Syphilis may be a cause of delayed resolution (chronic interstitial pneumonia) incidentally if such a patient is seen several months after the subsidence of the acute illness the diagnosis of pulmonary syphilis may be strongly suggested. Youmans and Kampmeier found that 13 of 31 patients with unresolved pneumonia and such post-pneumonic complications as pulmonary abscess and bronchiectasis had syphilis Weinstein and Goodman have reviewed the incidence of post-pneumonic complications in 509 patients with pneumonia (of whom 139 had syphilis 370 did not) from the Johns Hopkins Hospital. Though delayed resolution was no more frequent among the syphilitics, we are convinced that in some patients syphilis plays a causative rôle and that in such instances treatment hastens resolution. When a syphilitic patient develops pneumonia, treatment with neoarsphenamine or mapharsen should be started promptly after the crisis and continued throughout convalescence

We see no point in annoying a patient with proved (*S viridans*) subacute bacterial endocarditis with antisyphilitic treatment which is of no benefit to the septicemia the prognosis of which is hopeless or nearly so However recent experimental studies by Osgood may modify this gloomy statement.

Neoarsphenamine has been advised for the treatment of pyelitis by a

* The relatively high incidence of biologic false positive serologic tests in patients with acute upper respiratory infections (including pneumonia, especially if serum treated) must not be overlooked.

number of workers, among them Reucker and Chetwood. This drug is apparently superior to arsphenamine in this condition, possibly because of the inclusion of a formaldehyde radical in its molecule. We have had no personal experience with its use in pyelitis, but some urologists feel that occasionally it is of value. The association of pyelitis with syphilis is therefore an indication for continuation of specific treatment.

In treating patients with both gonorrhea and syphilis, the physician should know that in certain instances (at least in pre-sulfonamide days) the administration of the arsphenamines will cause an exacerbation of the urethral discharge. Since syphilis is the more important of the two diseases for the patient's ultimate health, the possible aggravation of gonorrhea should not, however interrupt treatment and there is no objection to the simultaneous administration of sulfonamides for gonorrhea.

Syphilis and granuloma inguinale.—These two conditions are frequently associated in our clinics. Neither arsenic, bismuth, nor mercury has any healing effect on the granulomatous lesions, which must be treated with antimony compounds (usually tartar emetic). For maximum therapeutic effect, this drug should be given intravenously in 1 per cent solution, 5–10 cc. every 2–3 days. Since the toxic effects of antimony are very similar to those of arsenic (Kolmer) we have hesitated to combine antisyphilitic treatment with treatment for granuloma inguinale, reserving the former until the prolonged administration of antimony (with or without the combined use of surgical procedures radium or deep x-ray therapy) has effected a cure of the granulomatous lesion. This implies 3–4 months of continuous antimony therapy after the lesion has healed, in order to prevent relapse. Antimony has little if any influence on the syphilitic infection. If the patient is actually ill because of syphilis, it may be wise to give several weeks of antisyphilitic treatment for symptomatic relief before starting antimony.

Syphilis and diabetes.—This subject has been discussed in Chapters XIII and XIX. Controllable diabetes is not a contra-indication to treatment for syphilis.

Syphilis and nephritis.—We can add little to the discussion of this topic provided in Chapters XIII and XIX. McFarland has studied the subject in some detail. He concludes that the arsphenamines may be used with almost complete safety in non-syphilitic nephritis but that the use of heavy metals (especially mercury) should be rigidly controlled by careful observation and frequent rest periods.

Syphilis and cirrhosis of the liver.—When these two diseases co-exist it is wise to assume even though definite proof be lacking, that the cirrhosis may be due to syphilis and to treat the patient in accordance with the discussion on hepatic syphilis in Chapter XIX.

Syphilis and thyroid disease.—Netherton's authoritative discussion of the association of hyperthyroidism and syphilis in 62 patients has replaced vague clinical impressions. He says:—"Our experience has been that cases in which syphilis is associated with hyperthyroidism respond to surgery as well as do cases in which syphilis is not present. Convalescence is not prolonged and when subsequent antisyphilitic treatment is

instituted, desirable results usually are obtained Although our series of treated cases is small we have not observed any marked benefit from preoperative antisyphilitic treatment and in some instances the patient has become worse. The delay necessary for the application of antisyphilitic treatment as a therapeutic test is great enough to cause serious myocardial damage in cases of active hyperthyroidism and is contra-indicated unless the syphilis is in the early stages." If preoperative treatment is given iodides should be employed if at all only in doses appropriate to the hyperthyroidism rather than to the syphilitic infection

Maher and Woelka remark on the favorable effects of thyroidectomy in patients with combined hyperthyroidism and syphilitic heart disease.

Hypothyroidism is not a contra-indication to energetic antisyphilitic treatment.* Thyroid extract should be given at the same time in doses appropriate to elevate the basal metabolic rate to normal.

Late syphilis and cardiovascular diseases Arteriosclerosis essential hypertension rheumatic heart disease —Neither arteriosclerosis essential hypertension, nor rheumatic heart disease are in themselves contra-indications to antisyphilitic treatment provided cardiac compensation and reserve are adequate. In all these conditions, however the physician must estimate the relative probable prognosis of the syphilitic infection and of the associated condition and plan his treatment methods accordingly In a patient with latent syphilis whose blood pressure ranges above 200/120 for example the chances of death in a few years from hypertension or its complications may be so much greater than from syphilis that little or nothing need be done for the latter The same is true of a patient with rheumatic or arteriosclerotic heart disease who has had repeated attacks of congestive heart failure. If on the contrary such a patient is ill from syphilis, with symptoms or lesions which treatment might improve he may be treated for symptomatic relief without fear of aggravating the cardiovascular lesion. In any case and especially after the development of congestive heart failure (with or without auricular fibrillation) the intensity of treatment should be milder than in the normal person i.e. neoarsphenamine or mapharsen in doses not exceeding 0 6 gm. or 0 04 gm. respectively with frequent rest periods. Neither bismuth nor mercury has so far as we know any deleterious effects on the cardiovascular apparatus and both may be utilized freely provided renal complications are not present.

Late syphilis and allergic diseases —Antisyphilitic treatment is well tolerated by patients with bronchial asthma, hayfever or other evidences of allergic instability We have seen no examples of sensitization to the arsenicals (dermatitis) appearing in such individuals in our clinics

Late syphilis and seborrheic or eczematous dermatoses —Patients with "sensitive skins " i.e. with pre-existing seborrheic or eczematous dermatoses are as Stokes points out, more likely than normal persons to develop cutaneous reactions to the arsenicals and are especially sensi

* Some caution is necessary in the interpretation of spinal fluid tests in patients with associated syphilis and myxedema, since spinal fluid protein is often considerably increased in the latter condition (Merritt and Fremont-Smith)

tive to mercurial inunctions Such individuals should be carefully watched during treatment.

Late syphilis and arthritis —We have been particularly impressed by the considerable number of patients in our clinics with apparently latent syphilis and subacute or chronic 'infectious' arthritis (usually arthralgia involving multiple joints, but without objective physical or x-ray alterations) in whom the institution of antisyphilitic treatment results in immediate symptomatic relief from the arthritis Similar spectacular relief has been observed in two patients with the Marie-Strümpell type of chronic ankylosing spondylitis. Whether this is due to a causative relationship between syphilis and the arthritis or to the non-specific effect of arsphenamine, is not clear At any rate treatment for syphilis has no deleterious effect on arthritides due to other causes than syphilis and may be of unexpected benefit.

Late syphilis and the anemias —This subject is discussed in Chapter XIX When syphilis is associated with secondary anemia of the chlorotic or idiopathic hypochromic type the patient should be treated with the daily oral administration of 8 gms. of ferric ammonium citrate, or an equivalent dose of another potent iron compound.

Late syphilis and obesity —Extreme obesity not only renders antisyphilitic treatment technically difficult but fat patients seem to tolerate the arsenicals less well, so far as mild reactions are concerned, than those of normal habitus. A patient who is 30 or more pounds overweight should be put on a 1200–1500 calorie reducing diet (Fishbein)

Surgery and syphilis —The following paragraphs are quoted from Keidel's discussion

'How should the surgeon proceed when confronted with the necessity for operation in a syphilitic patient assuming that the operation is for a condition not related to syphilis? This will vary depending on the stage of syphilitic infection and the type of operation. In untreated early syphilis (infections of less than two years' duration) and especially if the patient has infectious lesions, it is wiser to defer operation (surgical emergencies excepted) until the patient has had three months of treatment. This measure is for the protection of the surgeon and his assistants rather than for the sake of the patient. In the case of elective operations pre-operative treatment should include at least one course (8 doses) of an arsphenamine product and one course of intramuscular bismuth or mercury When this much has been given the patient may be operated upon regardless of whether his serologic tests are positive or negative. *As soon as possible* after operation treatment should be recommended, since, in early syphilis, continuous treatment, with no rest periods of any kind, is absolutely essential.

"If confronted with a surgical emergency in a patient with untreated early syphilis one must of course operate at once, with due regard to the safety of the operator and his assistants from accidental wounds. Something will be gained, if the patient s general condition justifies it, by giving 0 6 to 0 9 gram neoarsphenamine (or 0 04–0.06 gram mapharsen) before operation. As soon as possible after operation (second or third day)

regular treatment with neoarsphenamine or mapharsen should be started.

If the patient has a recent syphilitic infection which has been treated for at least three months or more with no lapses longer than one month prior to the development of a surgical complication there is no reason for deferring either emergency or elective operation If a lapse of more than one month has immediately preceded the desired operation, one should proceed as in an untreated early infection. As soon as possible in convalescence treatment should be begun again the type depending on the treatment given just before operation. Speaking generally it is wise to treat such patients while on the surgical service of a hospital with an arsphenamine rather than with bismuth or mercury

"It is essential for the surgeon in discharging a patient with early syphilis from surgical care to make arrangements for subsequent treatment to be carried on promptly and continuously either by the surgeon himself or by reference to another physician or a special clinic. This is a responsibility frequently overlooked, and failure to observe it may be fraught with the utmost disaster for the patient and his family

'When a surgical patient has syphilis of more than two years' duration, the surgeon should first assure himself by a careful general examination or by consultation with an internist, of the probable presence or absence of cardiovascular or central nervous system involvement, the presence of either of which may seriously modify the surgical risk involved in operation If the patient s general physical condition is good the presence of a syphilitic infection may be completely ignored so far as the question of the propriety of operation is concerned and this is true whether the serologic tests are positive or negative. *There is not the slightest reason for deferring operation until the blood tests are negative* * To accomplish this therapeutic result may take months or may even be completely impossible. Post-operative antisyphilitic treatment should however be administered to all such patients in order to prevent possible difficulty in wound healing. Such treatment need not be as intensive or as hurried as suggested for early syphilis two or three injections of neoarsphenamine while the patient is in the hospital are all that is necessary The surgeon s chief responsibility in these circumstances is to make sure that the patient knows he has syphilis that he realizes that other members of his family must be examined and that arrangements are made for continuing his treatment when he leaves the hospital.

Syphilis and trauma—wound healing —Many surgeons hesitate to operate on a patient with syphilis because of the possibility that the infection may play some part in retarding or preventing the healing of the wound. Undoubtedly instances do occur almost always in unrecognised and untreated syphilitics in which the operative wound breaks down refuses to heal or becomes the site of a syphilitic inflammatory process. The rarity of this occurrence however is pointed out by the fact that in most large surgical services literally hundreds of syphilitics are operated upon yearly without any knowledge by the surgeon before or after the operation that the patient has syphilis Goeckerman made a special study

* Italics ours.

of this point at the Mayo Clinic. He analyzed the post-operative course of 78 syphilitic patients, of whom 50 were treated for syphilis before or after operation and 28 were not. Three of the untreated group underwent operations on gummatous lesions one each of skin thyroid and cervical gland. In each the surgical result was disastrous. Only one of the 50 treated and 4 of the remaining 25 untreated patients had any post-operative difficulty whatever and in but 2 of these 5 could syphilis be even indirectly incriminated.

Syphilis and surgical risk —It is exceedingly difficult to evaluate the added surgical risk due to the presence of syphilitic infection In the average large surgical service where the Wassermann reaction is not routine large numbers of syphilitic patients are operated on without any marked increase in mortality or undue post-operative difficulty The occasional case does however, arise in which syphilis may play a large rôle in an unsatisfactory surgical result or in increased operative or post-operative mortality The surgeon who recognizes syphilis in his patients, clinically and by means of the routine blood Wassermann, and who has an appreciation of the anatomical and physiologic damage which syphilis may produce, is in a vastly better position to deal with this situation than his less well informed colleague

Syphilis and ununited fractures —There is no unanimity of opinion as to the rôle played by syphilis in the etiology of ununited fractures. Henderson as the result of a survey of several hundred cases feels that syphilis cannot often be incriminated. On the other hand Estes and Gellé cite a number of examples of non-union of fractures in syphilitic patients in some of which at least union occurred after the institution of antisyphilitic treatment. Personal experience with this question would indicate that most fractures in syphilitic patients heal quite as promptly as in normal individuals, but that in an occasional syphilitic union does fail to occur The results of antisyphilitic treatment in such patients are usually disappointing so far as rapid union is concerned, and one of the recognized orthopaedic operative procedures is usually necessary

Rarely one sees, in patients with easily recognizable neurosyphilis Charcot changes occurring in an ununited fracture Under these circumstances plating bone grafting and the like are usually unsatisfactory and the best one can hope for is support by a brace the worst amputation Certainly whether or not syphilis plays any real rôle in the mechanism of production of ununited fracture it occurs sufficiently often in syphilitics to make desirable an investigation for syphilis in all cases of bony non-union. Such an investigation should include as a minimum a complete physical examination with special attention to the nervous system and cardiovascular apparatus, a blood Wassermann test, and roentgenograms, not only of the site of the fracture but also of the shafts of the long bones involved This last is prompted by the fact that we have seen several instances in which the shafts of the long bones above or below an ununited fracture were the site of a definite syphilitic periostitis osteomyelitis or osteitis.

If syphilis is discovered to be present in a patient with an ununited

fracture at least 6 to 8 weeks of intensive antisyphilitic treatment should be given before any operative procedure is undertaken, and of course, treatment should be continued after operation.

Transfusion and syphilis —A large number of accidental infections with syphilis from blood transfusion have been reported and four* such instances have come under observation at the Johns Hopkins Hospital. It is of course routine practice everywhere to insist on negative serologic tests in the donor before transfusion. This is as much of a *sine qua non* as matched blood. Unfortunately in primary syphilis and in certain instances of relapsing or recurrent secondary syphilis, the serologic tests may be negative or may not have yet become positive In one instance in Baltimore a father was transfused with matched blood from his seronegative son and in another instance a son from a seronegative father and in each case the donor had at the time of transfusion a darkfield positive penile chancre of a few days duration Both recipients developed florid secondary syphilis in 4 to 6 weeks after transfusion It does not suffice, therefore to obtain negative serologic tests from the donor One must also ask the two questions 'Have you ever had syphilis?' and 'Have you recently had or have you now a genital sore of any description?' and the genitalia should be inspected.

"An unusual transfusion accident has recently been observed which suggests the necessity for caution in the various methods of direct transfusion. A nonsyphilitic donor in perfect health, volunteered blood for a seriously ill patient on whom no serologic tests had been done. During the operation by a closed direct method involving the use of large syringes, the apparatus jammed and the donor received some of the recipient s blood intravenously Five weeks later he developed secondary syphilis, with no sign of a chancre. At this point the recipient s serologic tests were found to be positive. There is no need to point the moral. (See Chapter III for a more detailed discussion of transfusion syphilis.)†

Psychoses and syphilis —In a psychotic patient with known late syphilis, it is of paramount importance promptly to determine whether the mental symptoms are due to paresis. This disease may produce symptoms which closely simulate those of schizophrenia or manic-depressive insanity differentiation can only be made on the basis of examination of the spinal fluid and sometimes not then. If the fluid shows the paretic formula, the patient had better be treated as if the diagnosis of paresis was certain (fever therapy—see Chapter XXIV) If the psychosis is clearly due to other causes than neurosyphilis, standard methods of treatment may be employed as indicated.

Syphilophobia —This distressing condition has been discussed in il-

* Now twelve.

† The liability of the physician in cases of transfusion syphilis has never been finally determined. The legal bureau of the American Medical Association has record of only one such suit [*Callahan v Hahnemann Hospital* (Calif) 26 P (2d) 606 35 P (2d) 536] Although this case was decided in favor of the defendant, appeal was granted but was not heard because of the death of the physician In the opinion of Dr A. R Moritz, Department of Legal Medicine of the Harvard Medical School, the legal responsibility rests with the physician ordering the transfusion.

luminating fashion by Gilman. The patient with syphilophobia is entitled to a single thorough examination at the hands of a syphilologic ex pert. If he is not reassured by the negative results of such an examination, as unfortunately few are, his further management should be under the direction of a psychiatrist

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Chapter XXVI

THE TREATMENT OF SYPHILIS COMPLICATED BY PREGNANCY THE ANTENATAL PREVENTION OF CONGENITAL SYPHILIS

Congenital syphilis is as nearly a preventable disease as smallpox. It can be wiped out completely or nearly so by the adoption of two simple procedures (1) the routine use of a diagnostic blood serologic test in all pregnant women, and (2) the adequate treatment of the syphilitic mother during pregnancy The demonstration of this fact constitutes one of the most brilliant achievements of preventive medicine

The staffs of the Obstetrical and Syphilis Clinics at the Johns Hopkins Hospital were among the earliest workers in this field under the direction of the late J W Williams and Keidel respectively Our early results, published by Williams have been amply confirmed by many investigators in various countries prominent among whom are Gammeltoft, McCord and his co-worker Roberts. The studies begun in our own clinics by Williams and Keidel have been continued and amplified during the ensuing twenty years and were reviewed in 1934 by Turner of our staff and by McKelvey from the obstetrical standpoint Certain modifications in McKelvey and Turner's results have been necessitated by the more recent contributions of Faber and Black, Christie Caffey and Ingraham. The present discussion is based on McKelvey and Turner's analysis of our own material representing nearly 1000 pregnancies in 644 syphilitic women, on Ingraham's recently compiled figures, and on the results of our own follow up studies of syphilitic women who have received their antisyphilitic treatment and obstetrical care since the introduction of the newer methods of diagnosis of congenital syphilis in the newborn.

The effect of pregnancy on syphilitic infection —Before proceeding to a discussion of treatment and its results it is essential briefly to review the relationships of pregnancy and syphilis. If a woman acquires syphilis just before coincident with or shortly after impregnation the usual manifestations of early syphilis are often completely suppressed or if present are milder in degree than in non-pregnant women or in men. This beneficial effect of pregnancy on syphilis is not limited to the early stages of the infection but often extends throughout the life time of the patient and affords a considerable degree of protection against the appearance of late lesions especially neurosyphilis (Moore Kemp) In fact as we have elsewhere shown (Chapter XVI) a properly controlled pregnancy may be a valuable therapeutic measure in the treatment of syphilis in women enhancing the probability of an ultimately favorable outcome.

The effect of syphilitic infection on pregnancy —The effect of syphilis on the outcome of pregnancy is the reverse of the beneficial effect of pregnancy on syphilis. Until a few years ago syphilis was the largest

single cause of fetal death. In the Johns Hopkins Obstetrical Clinic, prior to the institution of antisyphilitic treatment for infected mothers, 34.4 per cent of all fetal deaths were due to syphilis to say nothing of the tragedies of congenital syphilis in the surviving infants Some idea of the ravages of this disease may be gained from Table 98 where appears the

TABLE 98

THE INFLUENCE OF LATENT SYPHILIS ON THE PRODUCT OF CONCEPTION
(C.C.G as compared with Jeans series)

	Total pregnancies	Child healthy non-syphilitic	Outcome of pregnancy per cent			
			Child living congenital syphilis	Died in infancy	Miscarriage or still-birth	Induced abortion
C.C.G. series (women with latent syphilis)	1467	16.0	11.1	18.4	48.0	4.5
Jeans compilation from the literature, syphilitic women	2000–4000	16.6	24.0	30.2	30.2	—
Jeans' normal women	1712	76.0	—	15.0	9.7	—

status of the child in 1467 pregnancies in women with latent syphilis collected by the C.C.G as compared with a similar compilation by Jeans from the literature for syphilitic and normal women A syphilitic woman, untreated, has only one chance in six of bearing a live healthy infant, as compared with the normal woman s three chances in four

The recognition of syphilis in the pregnant woman The positive blood serologic test —Since in the average pregnant woman the most searching physical examination fails to reveal any evidence of the existence of syphilitic infection the best and usually the only way to recognize its presence is by means of the routine use of the blood serologic test. This is now current practice in almost all large obstetrical clinics the observed incidence of syphilis ranging, depending on the race and general type of clientele from 3–23 per cent. It should be current practice not only in clinic patients but in patients of the private class as well no considerations of social level, expense or confusion of moral with medical issues should be allowed to stand in the way of its performance in every pregnant woman. Only if syphilis is recognized in the pregnant woman can it be treated only if it is treated can congenital syphilis be prevented and in the vast majority of instances recognition of infection in the mother depends on the blood serologic test, and on nothing else.

The reliability of the serologic test for syphilis during pregnancy —There still persists a superstition wholly unwarranted that pregnancy is a frequent cause of false positive blood serologic reactions. This has been repeatedly demonstrated to be untrue but the fallacy will

not down. Pregnancy does not cause false positive blood serologic tests. A positive blood serologic test in the pregnant woman verified on repetition to avoid error in labeling or technique is as diagnostic of syphilis as in the male or non-pregnant female regardless of the presence or absence of a history or physical evidence of infection The physician who disregards such a verified test and withholds antisyphilitic treatment from the mother accepts a grave responsibility for which he may justly be held accountable.

The seronegative pregnant syphilitic woman —Studies based in large part on serologic results obtained prior to 1930 indicate that a seronegative syphilitic woman may give birth to a syphilitic child with a high degree of frequency Thus Williams from this clinic reported in 1922 that 43 of 109 infants born to seronegative syphilitic women were certainly and 7 others questionably syphilitic and of the 50 mothers of those infected infants 46 had never received any antisyphilitic treatment. The C C G in 1934 recorded 13 presumably certain or probable instances of syphilis among infants born alive and 45 dead born babies (data as to syphilis not available) among 182 seronegative mothers all but 18 of whom had had some previous treatment. Both papers were careful to record, however that in practically every instance in which a seronegative mother was delivered of a syphilitic infant, there was some mention of syphilis in the mother's history —she told a story suggestive of the lesions of early syphilis in herself she had had one or more syphilitic (or probably syphilitic) children in previous pregnancies or her husband had syphilis

With the increasing sensitivity of modern serologic tests (almost double that of 1930 and earlier) it is increasingly rare to observe a previously untreated seronegative pregnant syphilitic woman. The suggestion made in the first edition of this book that pregnancy might operate to reduce the reagin content of the mother's blood even so far as to cause a false negative test, has not been borne out by actual analysis Crosby and Campbell have shown that in early syphilis at least the average quantitative reagin titre is as high in pregnant as in non pregnant women or men. This increasing sensitivity in serologic tests is responsible for Ingraham s recent statement that the birth of a syphilitic infant to a seronegative mother is now a relative rarity In this opinion we concur insofar as it applies to previously untreated women

It must not be forgotten however that a pregnant syphilitic woman may have been rendered seronegative by treatment administered to her prior to pregnancy The C C G records the outcome as to the child in 164 such women among whom there were 34 dead births and 11 living but certainly or probably syphilitic infants.

It is unlikely therefore that the diagnosis of syphilis will be made *for the first time* by the birth of a syphilitic infant to a seronegative woman The relatively large number of previously treated and seronegative women registering in obstetrical clinics for prenatal care should however demand that every pregnant woman have not only a routine serologic test, but also careful inquiry for a previous history of syphilis or of treatment for it.

Whether to treat the seronegative syphilitic woman during a given preg-

nancy is a decision which calls for the closest judgment. It depends largely on three factors the duration of syphilis in the mother the amount and character of previous antisyphilitic treatment and the outcome of previous pregnancies. If the mother's infection is of more than 10 years' duration, if previous treatment has been adequate to permit the probation of the mother and especially if several uneventful and seronegative years have passed by since the termination of treatment and if one or more preceding pregnancies during which the mother has been allowed to go untreated, have resulted in living children known to be non-syphilitic treatment may be safely omitted. If at least two of these criteria cannot be satisfied, it is safer to treat the mother during the pregnancy in question in spite of the fact that her own blood tests may be repeatedly negative. It should be pointed out that habitual abortion, though obviously a reason for careful diagnostic investigation, is not necessarily due to syphilis and is not in itself a valid reason for treatment on suspicion during pregnancy

The serologically negative wives of syphilitic husbands The paternal transmission of syphilis —The consultant syphilologist is occasionally confronted with the problem of whether to treat the pregnant wife of a man known to have syphilis though the patient herself shows no historical physical or serologic evidence of infection. The solution of this problem depends on an understanding of the mode of infection of the fetus with syphilis which, while not yet entirely clear is almost surely by way of the maternal-fetal circulation For all practical purposes Colles' law may be dismissed as invalid the paternal transmission of infection, the mother being healthy does not exist* and the child in utero cannot be infected unless the mother herself has syphilis. If the marriage is recent and if the husband has had a recent infection with syphilis untreated or inadequately treated, his wife is likely also to be infected, and to develop within 2–3 months of infection, either physical evidence of the disease or a positive blood serologic test. Under these circumstances the pregnant wife had better be carefully watched with blood serologic tests repeated at intervals of every 2 weeks for at least the first 3 months of observation, and monthly throughout pregnancy thereafter treatment being withheld until the existence of syphilis is proved † These general comments also apply if the husband s syphilis is late rather than early the seronegative and physically normal wife need not be treated during pregnancy unless

* Unless the work of Levaditi, Warthin and others, suggesting a life cycle of the treponema which includes an infective granular form, is expanded and this hypothesis proved correct. Even under these conditions, the mother would almost surely be infected by the fetus, if she did not infect it and the paternal transmission of infection would be very rare.

† Several times we have encountered the circumstance that a man with dark field positive genital lesions has once or repeatedly had sexual intercourse with his pregnant wife The wives, examined within a few days after the last exposure, had no clinical or serologic evidence of infection. Though in general we do not favor the use of arsphenamine for chemotherapeutic prophylaxis, we employed it, apparently successfully in these women, on the grounds that the co-existence of pregnancy might suppress the lesions of early syphilis in the mothers, permit symptomless infection, and expose the fetuses to an undue risk. This is the only situation in which chemotherapeutic prophylaxis seems to us desirable (cf. Chapter XXXI)

there is strongly suggestive evidence of her own infection from her personal history or from previous pregnancies.

The time relationships of infection of mother and fetus.—Infection of the fetus depends largely on the time relationships of infection of the mother. If the mother acquires syphilis shortly before, at the time of, or shortly after conception, the fetus is almost sure to be infected *in utero*. Formerly it was generally felt, though so far as we know not definitely proved, that if the mother was infected after the sixth month of pregnancy, the fetus would probably escape intra-uterine infection. However, our own recent observation of several women probably infected during the second half of pregnancy suggests that the likelihood of infection of the fetus in utero in these cases is as great if not greater than when the maternal syphilis has been acquired nearer the time of conception. For this reason, the repetition of an originally negative blood serologic test at least once during the course of pregnancy (at about the seventh month) is especially recommended. When infectious lesions are present in the mother at the time of delivery, the infant may acquire the disease at birth by contact with such lesions during passage through the birth canal, or later by contact with lesions on the breasts or elsewhere. The probability that the child will be infected in utero diminishes somewhat as the years after the mother's infection pass by (Kassowitz's law). A woman who has had syphilis for many years may have completely normal children, though it is not safe to count on this to the exclusion of treatment.

The aims of antisyphilitic treatment during pregnancy.—The best available evidence indicates that infection of the fetus probably does not occur until about the fifth month of pregnancy or later,* and it is assumed that it occurs because of a regeneralization of the virus (spirochetemia) in the maternal blood stream which successfully passes the placental barrier. Treatment of the syphilitic pregnant mother may therefore accomplish either one of two aims: (a) prevention of infection of the fetus if treatment is begun early, before the fifth month, by means of destruction of treponemes in the mother's body and prevention of the wave of spirochetemia; or (b) if treatment is started later in pregnancy, after the fifth month, the actual early treatment of an already existing infection in the fetus, thus attaining the same desirable result as the very early treatment of acquired syphilis in the adult.

Studies by Eastman, Underhill and Amatruda, and Kraul and Bodnar have shown that arsphenamine and bismuth are retained in relatively large amounts by the human placenta, chiefly in the fetal portion; that the storage of drug is cumulative with successive injections; and that these drugs may also be found in fetal organs and blood after appropriate treatment of the mother. Snyder and Speert have recently demonstrated by animal experiments that following administration of arsenic to the pregnant mother in the latter half of pregnancy, there is a concentration of arsenic in the placenta, especially in the fetal portion; and that near term the arsenic content of the fetal tissues approaches the level calculated to

* This statement is based on the negative results of pathologic study of premature infants born before the fifth month.

be present in the maternal tissues. They conclude that placental transmission of the drug to the fetus is sufficiently great to be of importance in therapy

The transformation of the high probability of the birth of a syphilitic infant to the practical certainty of the birth of a normal living child is the first and major aim of treatment of the pregnant syphilitic woman, and this can be accomplished by treatment given actually during the pregnancy There are, however two additional aims of treatment (a) the protection of the fetus in possible future pregnancies, and (b) the cure or arrest' of the syphilitic infection in the mother A successful solution of these problems usually demands more treatment than can be given during the short space of the actual pregnancy

The methods of treatment During pregnancy.—It must be clearly recognised that treatment given during pregnancy is directed toward prevention or cure of syphilis in the fetus not in the mother Special features of the mother's infection as for example neurosyphilis must await the termination of the pregnancy What is desired is the maximum treponemicidal effect consistent with the safety of mother and child. Chief reliance should be placed therefore, on the arsphenamines, whose importance for the prophylaxis of congenital syphilis is clearly shown by Table 99 drawn from Gammeltoft's study As to the choice of a particular

TABLE 99

THE OUTCOME OF PREGNANCY IN SYPHILITIC WOMEN AFTER VARIOUS TYPES OF TREATMENT (AFTER GAMMELTOFT)

Treatment of mother	Cases	Percentage syphilitic children
None	201	96 5
Mercury before, none during pregnancy	87	89 6
Arsphenamine before, none during pregnancy	15	80 0
Mercury during pregnancy	111	72 0
Arsphenamine before, mercury during pregnancy	26	26 9
Arsphenamine during pregnancy	98	19 2
Arsphenamine before and during pregnancy	7	14 2

arsphenamine product, *there is to our minds an indication for the use of* arsphenamine (old salvarsan 606) even more definite than in early acquired syphilis, where the superiority of this product over other arsphenamines has been clearly demonstrated. However a comparison of our own arsphenamine results with the neoarsphenamine data of Roberts from McCord s clinic, fails to show any superiority for the former drug. It is probable that either product, given in large enough aggregate dosage will produce equally satisfactory results.

Our experience with the use of mapharsen as the arsenical of choice during pregnancy is too limited to permit us to draw any final conclusions regarding its value. Castallo and his co-workers report a discouragingly high proportion of syphilitic infants born of mothers treated with ma

pharsen during pregnancy Our impression also is that if mapharsen is to give results comparable with the arsphenamines it should be used during pregnancy in maximum doses twice rather than once weekly

Each of the three drugs arsphenamine neoarsphenamine or mapharsen should be given in average therapeutic dosage (0.3 gm. arsphenamine 0 6–0 75 gm. neoarsphenamine once weekly or mapharsen 0 060 gm. twice weekly to the average adult female) without undue regard for minor reactions such as transient nausea and vomiting a few hours of malaise etc. If treatment is started after the eighth month of pregnancy the arsphenamines may be given every 4–5 days mapharsen every 2–3 days. The length of the course will depend on the duration of pregnancy If early i.e. before the fifth month a course of 8 arsphenamine (or 16 mapharsen) injections may be followed by a short course (4–6 doses) of intramuscular bismuth, but treatment should always be planned so that the three to four weeks just prior to delivery are occupied by an arsenical rather than by a heavy metal. If the treatment is begun after the sixth month it should consist of weekly injections of an arsphenamine (or bi-weekly of mapharsen) *until delivery* *With this should be combined for reasons* presently to be shown a series of 6–8 weekly intramuscular injections of bismuth given on the same day as arsphenamine treatment. As in early syphilis treatment should be absolutely continuous without rest intervals of any sort until delivery The intensity of treatment cannot be relaxed during the final months of pregnancy merely because it may have been started early

Pregnant women stand this sort of intensive therapy equally as well as non-pregnant women or men. We do not agree with Ingraham s opinion as to the added hazard of antisyphilitic treatment during pregnancy In our own material, Peckham has shown that toxemias are actually less frequent in treated, pregnant syphilitic women than in non-syphilitic patients Naturally toxemia should be watched for (sclerae for jaundice urine and blood pressure) and treatment suspended for this cause if necessary It is true that certain rare and very grave treatment reactions (acute yellow atrophy hemorrhagic encephalitis) are more common in pregnant patients than in non-pregnant women or men but these are apparently unrelated to dosage, and are largely preventable by close attention to prodromal reactions.

There is no fear of harming the fetus by treatment. Occasionally when arsphenamine is given very late in pregnancy labor will be precipitated but early abortions and miscarriages will not occur as a result of treatment. Minor treatment reactions may be disregarded and the mother urged to undergo their discomfort in view of the great importance of obtaining a normal child This is one type of syphilitic infection in which a change in the drug or reduction in dosage for the sake of obviating an hour or two of nausea, are not justified.

These principles of treatment of the pregnant syphilitic woman are summarized briefly in Table 100

Spinal fluid examinations in pregnant women —The incidence of neurosyphilis symptomatic or asymptomatic, is much lower in

TABLE 100

THE PRINCIPLES OF TREATMENT OF THE SYPHILITIC PREGNANT WOMAN

1 Treatment during pregnancy is for the child, not for the mother Treat her later

2. The aim is *prevention* of infection in the fetus if pregnancy is early; its "cure" if late.

3. Use maximum treponemicidal attack throughout.

4. Arsphenamine (606) is better than other arsenicals in this instance. Use it when possible.

5. Give a minimum of 3.0–4.0 gms. arsphenamine (10–14 doses) if time permits—but no matter how late, give some arsphenamine.

6. Plan treatment so that it starts and ends with arsphenamine—a few doses just before delivery

7 Use some heavy metal—bismuth or mercury—in combination or alternation with arsphenamine.

8. Continuous treatment—no rest periods.

9. Don t *fear* treatment reactions unduly but watch the mother's sclerae, urine and blood pressure.

10. The fetus will not be harmed by treatment.

11 Study the infant by means of serologic and pediatric follow-up (*see text*)

12. Treat the mother's syphilis *after* delivery

women than in men, and lower in women who have been pregnant since infection with syphilis than in those who have not (Moore Kemp) However routine study of the cerebrospinal fluid is as indispensable a part of the management of latent syphilis discovered during pregnancy as of any other stage of the disease. In our own clinic we have avoided lumbar puncture during the actual duration of pregnancy partly because whatever its outcome it would not materially modify the treatment given at this particular time, which is directed toward the fetus rather than toward the mother partly because it is desired not to add to the already present manifold discomforts of pregnancy and of antisyphilitic treatment. Within a few days after delivery and preferably while the mother is still in bed lumbar puncture may and should be done, with a minimum of discomfort and with avoidance of the risk of post-puncture headache. Subsequent treatment of the mother's syphilitic infection will be partly based on the result.

The methods of treatment After delivery —There is usually a slight and often a long hiatus in treatment after delivery of the child. It is often difficult to persuade the mother usually symptomless and in the best of health, to continue treatment but if possible this must be done. It is particularly important if the mother s infection has been recent (within two years) and if the mother has had early syphilis discovered in the latter

This lesion has appeared in the skeletal x rays of the majority of our non-syphilitic infants whose mothers received antenatal bismuth therapy Whitridge, from this hospital, has produced bismuth lines in the long bones of normal infants by the bismuth treatment of non-syphilitic women during pregnancy

A second source of confusion was eliminated when Chiari and Caffey both clearly demonstrated that a wide variety of conditions in young infants may result in the appearance of roentgenographic skeletal lesions closely simulating the changes due to syphilis Applying these modern conclusions, it is now possible to re-arrange the 10 criteria of McLean as listed by Black for the x ray diagnosis of osseous syphilis. The four lesions that have not been demonstrated in non-syphilitic infants are as follows

1 "Well-defined saw-tooth metaphyses in well calcified bones
2. "Destructive lesions at the mesial or lateral aspects of the metaphyses (foci of rarefaction)
3 "Bilateral symmetrical osteomyelitis of the proximal mesial aspects of the tibiae
4 "Multiple 'separation of epiphyses' with or without impaction in bones which are not rachitic.

The other group of lesions formerly thought to be specific evidence of syphilitic infection are now recognized as non-specific. They have been demonstrated in non-syphilitic infants at various times during the first four months of life in a variety of combinations and due to a variety of causes (i.e. bacteremia due to staphylococcus pneumococcus and tubercle bacillus erythroblastosis fetalis, septic hemolytic anemia, familial hemolytic anemia multiple birth injuries congenital atresia of the biliary apparatus severe malnutrition unexplained hemiparesis, protozoan encephalitis, maternal bismuth therapy normal growth prematurity healing rickets and traumatic periostitis of the newborn)

The non-specific skeletal lesions are as follows

1 "Deep zones (in the longitudinal axis) of submetaphyseal rarefaction.
2. Multiple circumscribed osteomyelitis of the long bones shown by the roentgen rays as patchy areas of rarefaction.
3 "Multiple longitudinal areas of rarefaction (osteomyelitis) in the shafts of the long bones sometimes resulting in fractures.
4 Multiple areas of cortical destruction generally seen within a centimeter of the ends of the bones.
5 "Double zone of rarefaction at ends of bones.
6. "Localized periosteal cloaking occurring in more than one bone.

We are unable to confirm Ingraham s contention that extensive periosteal cloaking involving one or more long bones of the infant, which he observed usually after two months of age necessarily represents early rachitic involvement of the bone. We have seen it frequently in the initial x rays of babies from 2–8 weeks of age and with serial roentgenograms have watched its gradual disappearance before 4–6 months of age in infants whose antirachitic therapy from birth was adequate. In a number of such infants blood calcium phosphorous and phosphatase determina

tions failed to demonstrate rickets We believe that the lesions may possibly be a manifestation of normal growth processes.

The frequency of the occurrence of unequivocal osseous syphilis in the presence of negative serologic reactions has been a matter of debate We agree with Black that it must be extremely uncommon in early infancy and we have not seen a case in our observation with simultaneous serial x-ray and quantitative serologic tests of 400 infants of syphilitic mothers. As Ingraham points out, however "its occasional occurrence seems difficult to refute in the light of observations like those of McCord in which not only the abnormal roentgenogram but *S pallida* as well was demonstrable in 7 infants with negative results to serologic tests. It is important to note that all 7 of these children were dead, presumably from syphilis and that data concerning the mothers serologic tests at the time of delivery are not provided.

An enormous amount of investigative effort has been devoted in our own clinic and elsewhere, to the place of roentgenography in the diagnosis of infantile congenital syphilis We agree thoroughly with Ingraham and his group in their "opposition to the employment of this method as a routine diagnostic procedure for all offspring of syphilitic parentage." As we have seen the method used over a period of years it is expensive there is often complete disagreement in interpretation of the findings as between roentgenologist, pediatrician, and syphilologist In only the exceptional case are positive roentgenologic findings present in a seronegative child the information furnished by x ray is usually obtainable no sooner than the more valuable data supplied by the much simpler and less expensive serologic test.

While it seems desirable that further roentgenologic study of infantile osseous syphilis proceed in large clinics as a research problem we feel no hesitancy in advising the average practitioner to employ it only under exceptional circumstances and to be particularly guarded in its interpretation. In ordinary practice, serial roentgenography of the infant may well be limited to the offspring of untreated or grossly inadequately treated, syphilitic mothers who have never received bismuth. In Ingraham's experience, "the roentgenogram was found to be of some positive diagnostic value in 27 per cent of the instances in which the mother had had no prepartal treatment, in 10 per cent of the cases in which she had had less than two months of prepartal therapy but in no instance in which as much as sixteen weeks of prepartal treatment had been administered " Even in such cases the diagnosis of infection of the infant should never depend on the x ray alone, but on its correlation with clinical and serologic examinations.

It should be noted that our present condemnation of x-ray as a routine diagnostic measure is a complete reversal of the position expressed in the first edition of this book.

Darkfield examination of the umbilical cord —This is a method of immediate diagnosis of infection of the fetus living or dead, with which we have had no personal experience, but which is highly praised in Germany and has been successfully applied by Ingraham in this country It is

said that in most infants with congenital syphilis, treponemes may be found in the wall of the umbilical vein We quote the technique of the examination from Philipp who says on the basis of 120 cases 'After the cord is cut, a piece about 5 cm. long is taken from the peripheral end The cord vein is dissected out carefully freed from blood and with a scalpel some tissue juice is scraped from the inner vein wall This is diluted a little if necessary with normal saline and examined at once by darkfield The number of treponemes varies sometimes they are present in the first preparation sometimes it is necessary carefully to search 10–20 preparations.

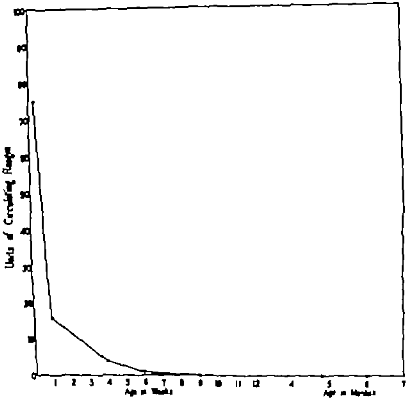
The examination is performed within a few minutes of birth. A positive result makes the definite diagnosis of congenital syphilis at once much sooner than is possible by the combined methods of serologic test, clinical observation x ray etc A negative result does not definitely rule out syphilis but merely makes it necessary to await the results of other examinations.

The procedure is strongly advised since so far as is now known a positive result permits an immediate diagnosis in the child

Serologic and clinical observation —With the recent increase in the number of women receiving prenatal antisyphilitic treatment there has been an increasing interest in the status of newborn children with no other evidence of syphilis than positive serologic tests Since as will be shown later these children are frequently non-syphilitic they form a group in which errors in the diagnosis of congenital syphilis have been common. This diagnostic problem has however been clarified to a great extent by the work of Fildes Faber and Black and of Christie on the quantitative estimations of syphilitic reagin in infant s blood.* These and other workers including ourselves have shown that normal (subsequently proved to be non-syphilitic) infants born of seropositive syphilitic mothers (treated or untreated) may have positive serologic tests in cord blood or in the venous blood withdrawn from the infant at or shortly after birth This phenomenon is for unknown reasons much more frequently observed when a complement fixation test is employed (in our material 113 of 292 patients) than if a flocculation technique is used (8 of another group of 158 patients) The quantitative titre of the blood of these non-syphilitic infants may be lower or equal to the titre in the mother's blood. If however serial quantitative serologic tests are done on the infant s blood at weekly intervals during the first few weeks of life the titre falls and reagin finally and permanently disappears. Such infants subsequently observed do not develop other evidence of congenital syphilis thus demonstrating the maternal origin of the infant s reagin. The maximum length of time for which maternal reagin has been observed to persist in the blood of a normal infant is 70 days (3 cases of our own series) Usually it disappears within the first month of life.

* In order to avoid the necessity for the technically difficult procedure of repeated venipuncture in infants, satisfactory quantitative microflocculation tests may be performed with a small quantity of blood (6–8 drops) obtained from a heel puncture in a capillary or small test-tube.

The fear that late lesions of congenital syphilis may develop in the group of apparently non-syphilitic infants with initially positive serologic tests which subsequently revert spontaneously to negative has been partially allayed by Ingraham's recent report that none of a group of 87 such infants developed evidence of late congenital syphilis during a six year period of observation. We have observed 22 infants with initially positive and subsequently negative serologic tests for a period of from 3 to



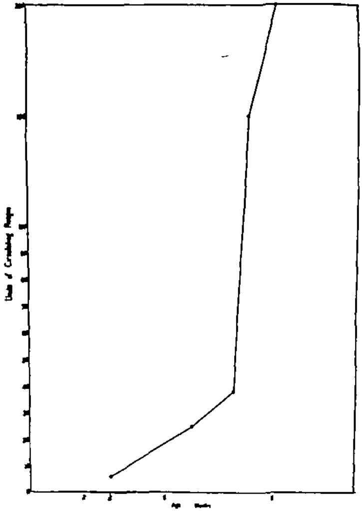
Quantitative Wassermann Titre of Blood of Untreated
Infants Whose Tests Became Negative

FIG. 83

4 years and so far none has developed late lesions of congenital syphilis. Similar prolonged follow-up studies are, however, still necessary.

If the child has been infected in utero, the cord and infant's blood at birth may be either negative or positive. If positive, it may remain positive at the same titre, the titre may rapidly rise, or in some instances the tests may revert temporarily to negative. However, no matter what the reagin titre is at birth or its course immediately thereafter, if the child is syphilitic, at some time before the 12th week, and usually by the 8th week, serial quantitative serologic tests will disclose the appearance of

increasing amounts of reagin in the infant's blood. The presence, therefore of reagin in the infant's blood at the end of the third month is indubitable evidence that the child is syphilitic.* The appearance of increasing amounts of reagin in the syphilitic child is usually associated with the development of definite clinical signs of syphilis (snuffles, darkfield positive



Quantitative Wassermann Titre of Blood of Untreated Infant Whose Tests Became Increasingly Positive

FIG. 83

* Since, for reasons as yet unexplained, maternal reagin in the infant's blood is more readily detected by a complement-fixation than by a flocculation technique, the routine use of the latter (to avoid unnecessary confusion) is recommended. In all the syphilitic infants we have observed, the flocculation technique has proved as sensitive as the complement-fixation test.

cutaneous lesions, osseous lesions etc.) all of which usually appear before the end of the third month of life.

In illustration of the foregoing general considerations we have followed with serial quantitative serologic tests 450 offspring of syphilitic women who received varying amounts of antisyphilitic treatment during their pregnancies. Three hundred and twenty nine infants had negative and 121 had positive serologic tests during the first month of life. The 329 have remained seronegative during a period of observation ranging up to 2 years. Of the 121 with positive tests, only 11 followed the serologic pattern of Fig. 83 with rising titre in later weeks and in all, the rising titre was associated with clinical evidence of syphilis. In some instances the clinical evidence was obtained only after the most careful x ray and clinical follow-up The remaining 110 became seronegative in from 2 to 9 weeks and have remained clinically and serologically well for periods of observation up to 2 years.

We feel, therefore, and in this regard are in agreement with other observers, that even in the absence of clinical or roentgenologic signs, every child whose serologic tests are positive at the end of three months, and possibly though of this we are not yet certain at the end of two months, may be considered with absolute certainty to be syphilitic. Conversely any child seronegative at the end of three months, no matter what the serum titre at birth may be as judged by experiences so far safely considered non-syphilitic, the initially positive tests being due solely to placental transmission of reagin. These conclusions are based on the desirable use of quantitative serologic tests. For the practitioner who does not have at his command a laboratory capable of accurate serologic quantitation standard diagnostic serologic tests will suffice We have observed no case in which the diagnosis of syphilis could not have been accurately made by the third month of life on the basis of qualitative flocculation tests.

The C C.G was able to compare the serologic tests of mother and child at the time of delivery in 441 women. When the mother's serologic test was then positive, the child s was likewise positive in 42 per cent of 234 cases. The majority of these children were subsequently shown to be non-syphilitic. On the other hand when the mother's serologic test at delivery was negative only 8 per cent of 207 infants (17 cases) had positive tests. Although the report does not detail the subsequent fate of these 17 infants it seems reasonable to assume, on the basis of our own much more limited experience of such cases that most if not all of these infants were actually syphilitic. Maternal reagin can hardly be transferred through the placenta when the mother has no reagin in her own blood. A seropositive child born of a seronegative mother is therefore to be followed much more closely and with more frequently repeated serologic tests (which now almost demand quantitation) than in any other situation.

Since in contrast to the elaborate diagnostic ritual outlined in the first edition of this book, we now feel that the average physician may rely almost *entirely on serial serologic testing of the infant for the diagnosis of* infantile congenital syphilis omitting more elaborate and esoteric pro-

cedures we have drawn up in Table 102 the possible serologic combinations which have been observed in mother and infant and have added an interpretation as to the final status of the infant. As knowledge stands at present, this is a satisfactory working guide.

TABLE 102

CORRELATION BETWEEN THE SEROLOGIC TESTS OF THE MOTHER AT DELIVERY OF THE INFANT AT BIRTH AND DURING THE NEONATAL PERIOD, AND THE ULTIMATE STATUS OF THE INFANT

Mother's serologic test at delivery	Infant's serologic tests		
	In cord or venous blood at birth	Subsequent tests over 3 months period	Final status of infant
Positive	Positive	Titre falls to permanent negative	Normal
		Titre remains unchanged or rises. Reverts to negative and later becomes positive	Syphilitic
	Negative	Remains negative	Normal
		Becomes positive in increasing titre	Syphilitic
Negative	Negative	Remains negative	Normal
		Becomes positive in increasing titre	Syphilitic
	Positive	Becomes negative recurs positive	
		Remains positive at same or increasing titre	
		Reverts to permanent negativity	Normal, or spontaneous cure of infant's infection

This is a purely hypothetical combination which we have never observed.

Shall every child of a syphilitic mother be treated for syphilis? —Opinion on this point is divided into three camps. Some observers like Welander feeling that in view of the difficulty in arriving at an early diagnosis of syphilis in the living offspring of syphilitic parents and of the fact that some congenitally syphilitic children develop no lesions in infancy attaining puberty or even early adult life before the explosion take the stand that every child born of a syphilitic mother should be treated whether or not it presents clinical or serologic evidence of disease Others like Wile think that treatment should be given only when some positive or suggestive evidence of infection is present, suggestive evidence being a positive cord serologic test or microscopic changes in the placenta.

Still others with whom we agree, feel that in such children treatment should be withheld until the presence of syphilis is definitely established.

Our reasons for this are several first, in the child as in the adult, antisyphilitic treatment is not without risk second serious social and economic problems are always created by attaching the diagnosis of congenital syphilis to any child and this is particularly true if the diagnosis is incorrect finally if all available methods of study are employed so that there is little delay in arriving at a diagnosis such delay as may occur does not materially jeopardize the child s chance of ultimate "cure" if treatment proves to be necessary Black is in accord with the impression that a delay of six weeks to two months in instituting treatment in an apparently healthy infant does not "jeopardize the chances of ultimate cure. Although Ingraham reports two cases in which the delay in instituting treatment may have been injurious (two infants dying at 16 and 25 days respectively while awaiting adequate serologic diagnosis), we believe that speed and thoroughness in applying the various criteria for establishing the diagnosis would eliminate nearly completely such untoward accidents.

The results of the treatment of syphilitic mothers at the Johns Hopkins Hospital expressed in terms of the outcome of pregnancy —The data concerning the outcome of the pregnancies of syphilitic women presented in the first edition of this book were based on McKelvey and Turner's detailed analysis of the Johns Hopkins material (1934) The incidence of syphilis shown in the infants of this study is unquestionably too high in the light of the more detailed information as to roentgenographic and serologic diagnosis provided above. In the study of Mc Kelvey and Turner the diagnosis of congenital syphilis in some infants was made on the basis of positive serologic tests at the age of 6 weeks, even in the absence of clinical signs, and in others on roentgenographic changes alone, without other confirmatory evidence. Certainly therefore some normal infants were regarded as syphilitic on the basis of maternal reagin in the blood or of non-specific x-ray changes.

However neither we nor other observers have as yet amassed a sufficient series of infants since newer knowledge crystallized and the series of McKelvey and Turner still stands as the best studied group available. In presenting a discussion of this material similar to that in the first edition therefore, we are speaking in default of more accurate data and with the understanding that the actual results as to normal living children are better to an unknown but very appreciable proportion than the figures presented. On the basis of present knowledge, we are reasonably sure that all the children designated by McKelvey and Turner as normal were actually so some of those regarded as syphilitic were normal also

In Table 103 is shown the outcome of 650 pregnancies occurring in women who had never received any antisyphilitic treatment prior to the pregnancy under consideration. The results are expressed in terms of children living or dead at delivery and of the ultimate status of the children based on necropsy results in children born dead or dying shortly after birth and in living children on x-ray evidence (when available) and

TABLE 103

OUTCOME OF PREGNANCY WITH VARYING AMOUNTS OF ANTISYPHILITIC TREATMENT. NO TREATMENT PRIOR TO PREGNANCY

(McKelvey and Turner)

Treatment during pregnancy	Number of pregnancies	Condition of child at birth, per cent		Ultimate status of child known, number of children	Of these, per cent	
		Living	Dead		Normal	Syphilitic
None	268	54.1	45.9	155	35.4	64.6
Arsphenamine less than 1.0 gm.	118	89.0	11.0	78	73.0	27.0
1.0–2.0 gms.	127	90.6	9.4	94	79.7	20.2
2.0–3.0 gms.	85	91.8	8.2	62	83.8	16.1
3.0–4.0 gms.	33	100.0	0.0	24	87.5	12.5
4.0–6.0 gms.	19	94.7	5.3	13	100.0	—
Total	650			426		

on clinical and serologic follow-up. In about a third of the infants these essential data are lacking; such children in whom information is not available are, of course, both syphilitic and normal infants, and although it is not fair to assume an equal distribution of syphilitic and non-syphilitic children in each unknown group, the influence of prolonged treatment of the mother in preventing congenital syphilis is nevertheless obvious from these data.

To show the effectiveness of various amounts of treatment during pregnancy, the results are expressed in terms of grams of arsphenamine (or their arsenical equivalent in silver or neoarsphenamine).* It is at once apparent that even relatively small amounts of arsphenamine administered to the mother during pregnancy enormously enhance the chance of obtaining a living baby, and that where it was possible to give as much as 4.0 gms. (an approximate average of 13–14 injections), congenital syphilis in the offspring was entirely eliminated.

McKelvey and Turner further approach the problem from another angle. One hundred and sixty-seven infants in their series were thought to have congenital syphilis. Of these, the mothers received no treatment in 100; only 16 mothers got as much as 2.0 gms. of arsphenamine (average 7 injections) during pregnancy. In most of these, treatment was either given at irregular intervals, or was omitted during the last few weeks of pregnancy.

* It makes little difference whether results are expressed in terms of doses or of grams of arsphenamine, since in our own clinic a fairly standard routine dose of 0.3 gm. was adhered to; thus, 1.0 gm. of arsphenamine means approximately three injections of the drug.

TABLE 104

INFLUENCE OF THE TIME OF ANTISYPHILITIC TREATMENT UPON THE OUTCOME OF PREGNANCY
(McKelvey and Turner)

Treatment of the mother	Number of pregnancies	Condition of child at birth, per cent		Ultimate status of child known, number of children	Of these, per cent	
		Living	Dead		Normal	Syphilitic
None	268	54.1	45.9	158	35.4	64.5
Before pregnancy only	83	81.7	18.3	46	91.3	8.6
During pregnancy only	391	90.0	10.0	260	81.5	18.4
Before and during pregnancy	202	93.1	6.9	135	95.5	4.5

TABLE 105

THE EFFECT OF TREATMENT OF THE MOTHER BEFORE PREGNANCY NONE DURING PREGNANCY UPON THE OUTCOME OF PREGNANCY
(McKelvey and Turner)

Treatment of the mother	Number of pregnancies	Condition of child at birth per cent		Ultimate status of child known, number of children	Of these per cent	
		Living	Dead		Normal	Syphilitic
Mercury only	3	66.6	33.3	1	—	100.0
Arsphenamine, less than 1.0 gm with or without mercury or bismuth	13	92.3	7.7	7	71.4	28.5
Arsphenamine 1–2 gms with or without mercury or bismuth	11	72.7	27.2	7	100.0	—
Arsphenamine 2–4 gms plus mercury or bismuth	19	89.4	10.5	12	100.0	—
Arsphenamine more than 4.0 gms. plus mercury or bismuth	29	82.7	17.2	18	100.0	—
Exact amount not known	7	57.1	42.8	1	—	100.0

Satisfactory as are the results of adequate treatment *during* pregnancy these are considerably improved upon when the diagnosis of syphilis had been made in the mother and some treatment given *prior* to the

pregnancy as well as during this period. Taking the material as a whole, the data of Table 104 indicate that the proportion of syphilitic infants is almost as low when the mother was treated before but not during pregnancy as when treatment was given at both periods of time (8 6 as compared with 4.5 per cent) In the latter case however the proportion of children living at birth is significantly higher (93 1 as compared to 81 7 per cent) Furthermore if one analyzes treatment given before pregnancy on the basis of the total amount of arsphenamine as in Table 105 it appears that of 59 mothers who received more than 1 0 gm. (3+ injections) of arsphenamine *prior* to but no treatment *during* pregnancy not one had a syphilitic baby The interval between treatment and the occurrence of pregnancy in these women ranged from a few weeks to several years.

The fact that a syphilitic woman has received treatment prior to pregnancy should not however prevent the administration of further treatment during the pregnancy especially if the mother is a primipara. While the probability of a normal baby is enhanced by the prior treatment it is almost certainly assured by adequate prenatal treatment. The beneficial effect of prior treatment is of importance in considering the potential outcome of possible further pregnancies as will be presently indicated.

As Wile and Shaw have pointed out and as McKelvey and Turner also found the results of treatment as regards the child were slightly worse when the mother had been recently infected (early syphilis) than when she had late or latent syphilis but even in early maternal syphilis as much as 4.0 gms arsphenamine during pregnancy afforded complete protection to the fetus

A point of great practical importance is whether treatment during pregnancy should be limited to the use of an arsphenamine product or whether a heavy metal should be added. The material furnished by McKelvey and Turner summarized in Table 106 furnishes a suggestive

TABLE 106

THE EFFECT OF THE ADDITION OF HEAVY METAL TO ARSPHENAMINE THERAPY DURING PREGNANCY ON THE ULTIMATE OUTCOME IN THE CHILD
(McKelvey and Turner)

Treatment of the mother during pregnancy	Number of pregnancies	Condition of child at birth, per cent		Ultimate status of child known, number of children	Of these, per cent	
		Living	Dead		Normal	Syphilitic
Arsphenamine alone 2.0 gms or more	60	90 0	10 0	41	78 0	22 0
Arsphenamine 2 0 gms. or more plus mercury or bismuth	78	96 1	3 9	61	93 4	6 5

answer When a heavy metal (mercury or bismuth) is given in addition to arsphenamine the proportion of living births is higher (96 1 as compared

with 90 per cent) and the incidence of syphilis in the offspring lower (6.5 as compared with 22 per cent) than when equivalent amounts of arsphenamine are administered alone. In this particular series of patients, *the two drugs were used in alternating courses when time permitted* and the mothers who received arsphenamine alone were usually so treated because they first came under care so late in pregnancy that there was no available time to follow a course of arsphenamine with a course of a heavy metal. The superior results when this was done, however clearly indicate the desirability of combined therapy during pregnancy If treatment can be started early enough (before the fifth month) to permit alternating courses, this alternation should be carried out. If treatment must be started later than the seventh month the two drugs should be given in combination, e.g., a weekly injection each of arsphenamine and bismuth given on the same day

The superior results of starting treatment early in the course of pregnancy are apparent from Table 107 again summarized from McKelvey

TABLE 107

THE OUTCOME AS TO THE CHILD AS INFLUENCED BY THE TIME OF STARTING TREATMENT IN THE MOTHER: THE PREVENTIVE VERSUS THE CURATIVE TREATMENT OF INTRAUTERINE CONGENITAL SYPHILIS
(McKelvey and Turner)

Treatment of the mother started during	Total pregnancies	Condition of child at birth, per cent		Ultimate status of child known, number of children	Of these, per cent	
		Living	Dead		Normal	Syphilitic
1st to 5th months inclusive	74	90.5	9.5	57	91.2	8.7
6th to 10th months inclusive	313	89.5	10.6	220	77.7	22.2

and Turner The chances of obtaining a living child are about equal whether treatment is started early or late but if it is begun within the first five months of pregnancy the chance of the birth of a syphilitic baby is about one-third as great (8 7 per cent) than when it is delayed till the sixth month or later (22.2 per cent) It is of great importance to note, however as shown in Table 108 that even if the start of treatment is delayed as late as the ninth month the results as to the child are materially better than if no treatment has been given (per cent of children living at birth 87 5 as compared with 54 1 and of syphilitic infants only 24.5 as compared with 64.5 per cent) Though prevention of infection in the fetus (i.e. with treatment begun before the fifth month) is easier than its "cure" when once it has occurred (i.e. with treatment started later) nevertheless something of value may be accomplished no matter how late in pregnancy the existence of syphilis is recognized in the mother Even if she is almost at term an injection or two of arsphenamine may materially improve the infant's chance of life.

TABLE 108

THE EFFECT OF TREATMENT LATE IN PREGNANCY AS COMPARED WITH NO TREATMENT IN THE OUTCOME AS TO THE CHILD

(McKelvey and Turner)

Treatment of the mother during pregnancy	Total pregnancies	Condition of child at birth, per cent		Ultimate status of child known, number of children	Of these, per cent	
		Living	Dead		Normal	Syphilitic
None	268	54.1	45.9	155	35.4	64.5
During 9th and 10th months only	168	87.5	12.5	117	75.4	24.5

The spontaneous cure of congenital syphilis—Ingraham and his co-workers like ourselves have realized that many infants who would have been regarded as syphilitic on the basis of the criteria of 10 years ago are actually normal. They have recently reviewed the later status of 59 infants diagnosed as syphilitic in 1933–1935 Their material is summarized in Table 108a. They say "Perhaps the most striking revelation of [this] table aside from the indication that the mortality rate approaches zero for those infants who received active therapy for a year or more is the fact that the offspring who were diagnosed as syphilitic in infancy only to remain untreated have fallen sharply into two categories on subsequent study (1) those who died as a result of syphilis and (2) those who survived with no clinical or serologic evidence of the disease. It will also be noted that a large percentage of the infants diagnosed as syphilitic but subsequently treated inadequately according to most accepted standards likewise became clinically and serologically normal.

TABLE 108a

COMPARISON OF STATUS AT THE END OF OBSERVATION OF FIFTY NINE INFANTS DIAGNOSED AS SYPHILITIC AND ADEQUATELY FOLLOWED AS COMPARED WITH AMOUNT OF POSTNATAL TREATMENT FOR CONGENITAL SYPHILIS

(1933 TO 1935 SERIES)

(From Ingraham et al.)

Status of Infant	Postnatal Treatment		
	None	Inadequate (Average 8.4 Wk.)	More Than 1 Year of Active Therapy
1 Clinically and serologically cured	12	12	15
2. Still showing signs and symptoms of syphilis and/or positive serologic reaction of blood	—	3	3
3. Died as a result of syphilis	10	3	—
Total	22	18	18

"An adequate study of these infants improperly diagnosed or self cured,' as the case may be, is rendered difficult by a lack of knowledge of the frequency of spontaneous cure of congenital syphilis and of the temporary or permanent remission of clinical symptoms and disappearance of laboratory evidence after a short course of therapy Such spontaneous remissions are known to occur in the adult with acquired syphilis but the severity of the disease as one is apt to picture it in the untreated infected infant has largely precluded any such considerations when one thinks of the congenital infection There has even been at times, a tendency to attribute the rapidly favorable response of infantile congenital syphilis in some cases to inadequacy of diagnosis rather than to the effectiveness of treatment."

They cite two well-documented cases of apparent spontaneous cure" of infantile congenital syphilis following intercurrent hyperpyrexia of infectious origin.

Apparently Ingraham and his group feel that in the untreated and poorly treated infants diagnosed as syphilitic in 1933–1935 and found to be normal some 4–5 years later spontaneous cure is more likely than original erroneous diagnosis Our own impression would be the reverse. Though we are quite prepared to concede that spontaneous "cure of the congenital as well as of the acquired infection may occur (cf Chapter III) we think that it is probably a relatively infrequent phenomenon. Certainly the possibility has no practical importance in the management of the syphilitic infant.

The malaria treatment of prenatal syphilis —Certain German investigators among whom is Klaften, have utilized fever therapy especially malaria, in the treatment of pregnant syphilitic women, with it is claimed, good results as to the outcome of pregnancy Klaften reports the results as to the fetus in 23 women who had been treated with malaria prior to and in 18 during pregnancy In 17 of the former and 9 of the latter the infant was normal in the remainder it was syphilitic. These results are, however not as good as those obtainable with combined arsphenamine and heavy metal during pregnancy in addition, malaria therapy carries with it a distinct risk to life. We do not therefore advise it even in case the mother has neurosyphilis. Under these circumstances much the safer thing to do both for mother and child, is to administer arsphenamine during pregnancy reserving the malarial treatment of the mother s neurosyphilis until after delivery

Is it necessary to treat a syphilitic woman during every pregnancy?—A debatable and important practical point for decision is whether it is desirable or essential to administer antisyphilitic treatment to a known syphilitic woman during every pregnancy which she may have regardless of her own clinical or serologic status or of previous treatment. McKelvey and Turner's study throws some light on this problem. Included in their series are 59 mothers who had been treated for syphilis *before* pregnancy with a minimum of 1 0 gm. of arsphenamine with or without concomitant heavy metal (Table 105) and who either purposely or inadvertently were allowed to go through a subsequent pregnancy

TABLE 109

SUGGESTED OUTLINE OF TREATMENT OF THE PREGNANT SYPHILITIC WOMAN (Assuming that the mother's infection has been detected at about the fourth month of pregnancy)

Week	Treatment: Arsphenamine	Treatment: Bismuth	Remarks
1	0 3		Not necessary to start with small doses. Attack! Use arsphenamine in preference to other arsenicals. If neoarsphenamine must be used, make dosage 0.6–0.75 gm. not less. If mapharsen is used, give maximum dose (0.060 gm.) twice weekly *Watch scleras for jaundice, and urine and blood pressure for impending toxemia.* Treatment of this intensity will not cause abortion or miscarriage. Plan length of bismuth course (6–10 doses) so that treatment ends with a course of arsphenamine just before delivery If treatment is started early in pregnancy alternate 606 and bismuth. If it is started as late as the 7th month, combine the two, a weekly injection of each given on the same day for at least 6 doses of bismuth. Always provide an arsphenamine phase of treatment just before delivery If treatment is started as late as the 7th month, give arsphenamine weekly until delivery (10–14 doses) plus at least 6 doses of bismuth. If treatment is started as late as the 9th-10th month, give arsphenamine plus bismuth every 4–5 days. *Try to give at least 10 doses (5.0 gms) arsphenamine during pregnancy*
2	0 3		
3	0 3		
4	0 3		
5	0 3		
6	0 3		
7	0 3		
8	0 3		
9		0 2	
10		0 2	
11		0 2	
12		0 2	
13		0 2	
14		0 2	
15	0 3		
16	0 3		
17	0 3		
18	0 3		
19	0 3		
20	0 3		
21	0 3		
22	0 3		
During puerperium	(1) Careful serologic and pediatric observation (2) Test mother's spinal fluid as a routine.		
After puerperium	(1) Follow baby with repeated serologic tests for at least 6 months. (2) Resume treatment for mother according to stage of her infection i e early latent, neurosyphilis, etc See outlines in appropriate chapters.		

without treatment. Though the percentage of infants born alive was slightly less than in women treated during pregnancy there were no observed instances of syphilis in the infants live or dead.

In the C C G material were 52 women who became pregnant *after* an amount of treatment adequate to justify their classification as "cured." Though no treatment was given during the pregnancy none of the children was syphilitic

McKelvey and Turner conclude and we agree that thorough treatment of the maternal syphilis *prior* to pregnancy i.e. not less than 4 gms. of

arsphenamine with appropriate heavy metal, probably affords adequate protection of the offspring in subsequent pregnancies even though treatment during the pregnancy is omitted. They feel however that if the maternal serologic test remains positive or if there is clinical evidence of persistent infection, it seems wise to treat the mother during pregnancy regardless of the amount of previous treatment.

Suggested outlines of treatment for syphilitic women during pregnancy —We append as Table 109 a tabular summary of suggested treatment for the pregnant syphilitic woman As with early syphilis, it would be wise for the practitioner to adhere closely to this scheme without attempts at individualization unless these are necessitated by such complications in the mother as toxemias of pregnancy a previous post-arsphenamine dermatitis, cardiovascular syphilis hypertensive cardiorenal disease, rheumatic heart disease or tuberculosis. In any one of these events treatment must be materially modified, and the added risk to the infant accepted.

May a syphilitic woman nurse her infant?—Whether the apparently normal newborn infant of a syphilitic mother may be fed at the breast depends on the time relationships of the mother's infection on the amount of treatment given to the mother before delivery and on the probability of her continuing treatment after delivery We have seen mothers with active early lesions who had failed to report to the hospital until within a few days of labor or actually after its start. It is usually possible to give at least one dose of arsphenamine to such women which will decrease the probability of the infant s infection during birth. *But the infant should not nurse* the breasts either of its mother because of the fear that if normal it may be infected by her or of a wet nurse because of the fear that the infant may actually be syphilitic and may infect her Such babies should be fed artificially from the start.

If the mother has had 6 or more injections of arsphenamine during pregnancy, it is safe for her to nurse her normal infant provided her own infection is recent, and that she continues treatment as promptly as possible after delivery in order to guard against infectious relapse (we have seen two instances of chancres of the lip in infants from failure of such mothers to understand the necessity for further treatment) or if her infection is of long standing (4 years or longer) regardless of further treatment, though this should not be neglected.

The syphilitic infant should of course be breast fed when possible. Breast eeding is not a substitute for antisyphilitic treatment of the infant such minute quantities of the drugs given the mother are secreted in the breast milk that the infant receives little or no benefit in this manner

Therapeutic abortion Sterilization of a syphilitic woman —We have never seen an instance in which therapeutic abortion seemed justified because of syphilis in the mother though such a circumstance might arise in the event of pregnancy occurring in a woman with grave hepatic or renal syphilis. So far as the child is concerned, the results of antenatal treatment are too good to justify the procedure. In the occasional prolific syphilitic female (usually Negro) who is at the same time

wholly uncooperative as regards treatment during pregnancy and who has already borne a half dozen or more syphilitic infants sterilization is strongly advised.

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wholly uncooperative as regards treatment during pregnancy and who has already borne a half dozen or more syphilitic infants sterilization is strongly advised

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infection. It seems to us as important to make this distinction in congenital as in acquired syphilis. The lesions typical of early congenital syphilis (i.e., in infants under 2 years of age) are entirely analogous, from the clinical standpoint to those occurring in early acquired syphilis in adults. Most infants in whom the infection is clinically recognizable at all have lesions of a secondary type In contradistinction to acquired syphilis in adults, however the syphilitic infant suffers from a severe toxemia and concomitant lesions in the viscera, especially liver spleen bone marrow kidneys and lungs as a part of the strikingly heavy infection with organisms. The constitutional disturbances are therefore far more profound than in the acquired infection the risk of death before the body's own defenses can be mobilized is grave instead of trivial as in adults. The mortality rate among infants with untreated congenital syphilis is from 25–50 per cent (Jeans and Cooke) Important factors influencing the mortality rate are prematurity the severity of the infection, malnutrition, a lowered resistance to secondary infection and the time relationships, character and amount of treatment.

If the infant, unrecognized as syphilitic and therefore untreated survives the first few months of life, opportunity is provided for a mobilization of his own body defenses and he usually enters upon a period of latency of several or many years duration, terminated by the development of lesions involving particularly four structures —the eye the bones the inner ear and the nervous system. (The distribution of lesions in early and late congenital syphilis is shown in Table 110) Meanwhile, the prognosis as to life has undergone a marked change. There is little or no risk of death from late congenital syphilis unless there is involvement of the nervous system.

Thus in early congenital syphilis the aim of treatment is two-fold — the actual preservation of life, and, as in early syphilis in the adult, the symptomatic, serologic, and biologic—in other words the radical— cure of the infection, if possible. The available evidence indicates that both these ends may be accomplished.

In late congenital syphilis, on the other hand as in late acquired syphilis, radical "cure" is probably no longer attainable. The aims of treatment therefore become symptomatic relief the healing of lesions the prevention of the development of fresh lesions and the maintenance of good health and physical efficiency

A method of treatment of early congenital syphilis —The Drugs Employed —The arsenical preparation of choice for early congenital syphilis is sulpharsphenamine. The toxic sequelae of the use of this drug which preclude its use in adults are much less frequent in infants and young children indeed infants tolerate all arsenical drugs in relatively higher dosage than do adults. The particular advantage of sulpharsphenamine in infantile syphilis is that it may be given intramuscularly in concentrated (33 per cent) solution, thus obviating most of the physical struggle of treatment. The dosage is calculated on the basis of body weight, the initial dose usually 15 mgm/kg. subsequent doses 25 mgm/kg

The use of arsphenamine (606) in infants or young children is nearly

TABLE 110

THE INCIDENCE OF LESIONS IN EARLY AND LATE CONGENITAL SYPHILIS
(After Jeans and Cooke, and F R. Smith, Jr)

		Total number of children	Per cent in whom the infection was manifested by								
			Early skin or mucosal lesions	Rhinitis	Bone & joint lesions: Early	Bone & joint lesions: Late	Neuro-syphilis (clinical)	Eye lesions	Deafness	Other	Latency
Early (children under 2 years of age) Jeans and Cooke		610	81 1	59 9	16 3	—	4 9	1 1	—	1 9	16 3
Late (children over 2 years of age)	Jeans and Cooke	707	2 4	—	—	14 5	7 0	31 0	1 8	2 8	53 4
	Smith	462	—	—	—	27 4	5 1	54 5	13 6	7 5	38 8

impossible owing to the technical difficulties of intravenous administration. Mapharsen (in a dose of 0 75–1 0 mgm/kg) or neoarsphenamine (in a dose of 15 mgm/kg) may be used if desired, but these drugs too must be given intravenously into a superficial vein, thus increasing the technical difficulty of treatment. The longitudinal sinus (by way of the anterior fontanelle) should never be used for intravenous injections, even by the expert. We know of two instances of death from infiltration of the brain substance with neoarsphenamine. The intraperitoneal and rectal routes of administration are also not advised, the first because of its danger the latter because of therapeutic inefficiency

Of the two heavy metals either bismuth or mercury may be used. In our clinic, the former is now employed almost exclusively but in very young infants especially if malnourished mercury may occasionally be preferable. It is given as inunctions of U.S P (50 per cent) mercury ointment. The dose is 1 gm. daily placed on the inner surface of an abdominal binder which is allowed to remain on the baby during the day We do not advise the administration of mercury by mouth (usually given as mercury with chalk, gray powder Hydrargyrum cum creta, dose 12–32 mgms. three times daily) partly because of therapeutic inefficacy partly because of difficulty of administration to infants and partly because of its tendency to cause gastro-intestinal upsets Intramuscular injections of mercury are also inadvisable because of danger of toxic effects.

Bismuth is easily utilizable, even in infants, if the muscle mass of the buttock is large enough to tolerate repeated intramuscular injections. As in adults the subsalicylate in oil is advised in a dosage of 2–4 mgm/kg.

Iodides are unnecessary in early congenital syphilis.

These drugs should be used in alternation, and treatment given continuously without rest periods of any sort, as in early acquired syphilis. The principle of treatment is the same, i.e to replace by means of chemotherapy the patient s own defense mechanism which has not as yet developed and which is prevented from developing further by the very fact of treatment. Of course, the continuity of treatment may at times be interrupted for short intervals by such pediatric difficulties as digestive disturbances or intercurrent infections.

Generally speaking treatment should start with the arsenical rather than the heavy metal phase. Therapeutic shock is more important than in the adult because of the intensity of the infantile infection and the first dose should be small (5–10 mgm/kg.) rapidly increasing to the desired maximum of 25 mgm/kg Rarely an infant is in such poor general condition as to make it seem likely that it will not survive even a slight therapeutic shock in such instances, 2–3 weeks of preliminary bismuth or mercury treatment will sometimes do wonders.

A suggested outline of treatment for early congenital syphilis, based in part on our own experience and in part on the literature, is presented in Table 111

The duration of treatment should be measured, as in the adult, by serologic control Since blood for testing is obtained from infants with some difficulty tests need be repeated only at the beginning of each arsenical

TABLE 111

SUGGESTED OUTLINE OF TREATMENT FOR EARLY CONGENITAL SYPHILIS

Week	Drug	Dose	Remarks
1	Sulpharsphenamine	5–10 mgm/kg	Test blood. Avoid therapeutic shock.
2–7	Sulpharsphenamine	25 mgm/kg	
8–11	Mercury by inunction daily or Bismuth subsalicylate weekly	1–2 gm. 2 mgm/kg	
12–19	Sulpharsphenamine	25 mgm/kg	Test blood *Do not stop treatment when serologic tests become negative.*
20–25	Mercury or bismuth		
26–33	Sulpharsphenamine	25 mgm/kg	Test blood. Also test spinal fluid at about this time
34–41	Mercury or bismuth		
42–49	Sulpharsphenamine	25 mgm/kg	Test blood. Note gradual lengthening of heavy metal course 4, 6, 8, and now 10 weeks.
50–59	Bismuth or mercury		Test blood. This is absolute minimum of treatment, which should be continued longer if necessary to fulfill serologic standard. Test blood every 6 months. Test cerebrospinal fluid at end of year
Thereafter	Prolong follow-up with physical and serologic re-examinations every 6–12 months until puberty is passed and, if possible, thereafter at least until early adult life is reached.		

course. The spinal fluid should be examined routinely as in early syphilis in adults. In the large series of Jeans and Cooke the incidence of asymptomatic neurosyphilis in early congenital syphilis was 23 4 per cent. Lumbar puncture* should be delayed until at least 6 months of treatment has been given if the fluid is normal it need not be repeated until the end of the year of probation. Treatment should be continuous in alternating courses of arsenical and heavy metal for a year after serologic negativity is achieved At the end of this time the patient may be placed on probation provided the cerebrospinal fluid is negative and there are no clinical signs of activity of the infection The absolute minimum amount is four courses each of sulpharsphenamine and heavy metal over an average period of 12 months. It is probable that this amount of treatment suffices whether or not the blood serologic test becomes negative.

This plan of treatment is subject to modification providing only that the three principles of alternating continuous and prolonged treatment

* Lumbar puncture headache in infants and young children apparently does not occur and subsequent rest in bed is not obligatory as in adults.

are maintained. It is subject also to modification on the basis of treatment reactions the development of neurosyphilis (see below) and the occurrence of intercurrent diseases. Obviously it is impossible to suggest alternatives for all possible contingencies which may arise the physician must proceed on the basis of his knowledge of pediatrics and by analogy with the complications of treatment developing in adults.

The results of treatment in early congenital syphilis —There are much less satisfactory data as to the ultimate outcome of treatment in early congenital than in early acquired syphilis. In thirteen reports surveyed by Whipple and Dunham, and in six more recent reports there were more than 2,200 children diagnosed as syphilitic and treated by well established methods before the age of 2 years. Of this total only one-fourth were adequately treated and followed long enough to determine the results of treatment. 'Fifty five to one hundred per cent of clinical and serologic cures are recorded in these reports but no constant relation appears between the method of treatment and the percentage of cures It is impossible, considering all the variables in the statistics to draw any conclusions concerning the relative therapeutic efficiency of the treatment systems used.

TABLE 112

RESULTS IN THE TREATMENT OF EARLY CONGENITAL SYPHILIS

(Jeans and Cooke)

Total children treated 6 months or more	During subsequent observation period of at least 3 years, per cent	
	"Cured"	Not "cured"
125	72 0*	28 0†

* Including 20 children with known neurosyphilis.
† Including 12 children with known neurosyphilis.

The largest and best-studied series seems to be that of Jeans and Cooke presented in summary in Table 112. The children in this group were treated by a plan similar to that in use in our own clinic. These authors say "Most of these children (under the age of 2) were treated for a year or less, but a few were given as much as two or three years' treatment. Those who are termed cured have remained serologically negative and free from clinical syphilis for at least three years most of them for a much longer time It will be seen that almost three-fourths of such a group were cured. This disregards the patients who died from intercurrent infections during therapy and therefore does not give a true estimate of the prognosis for infants who are treated adequately It is evident, however that a considerable proportion of infants who receive from six months to a year's treatment develop persistently negative Wassermann reactions and remain free from clinical manifestations of active syphilis In the infants who were so cured the presence of a positive Wassermann reaction in the spinal fluid before treatment did not appreciably prolong the period of therapy the spinal fluid becoming negative in a relatively short time.

That the biologic cure of early congenital syphilis may be accomplished is shown by Hahn's report from this clinic of two verified examples of reinfection with syphilis in adults who had received competent early treatment for infantile congenital syphilis. As babies treated 15 to 20 years ago reach adult life such instances may be expected to multiply.

It is not entirely clear either from our own experience or from the literature whether the adequate treatment and presumed cure of early congenital syphilis will prevent the later development of such stigmata as cranial bossing, Hutchinson's teeth, etc. Meyer suggests that under such circumstances stigmata fail to appear and we have not observed them in any adequately treated child.

A method of treatment for late congenital syphilis.—The principles of treatment are the same as in late acquired syphilis. The aim of treatment is symptomatic relief and maintained good health, relatively little emphasis being placed on serologic reversal. With minor modifications in drugs or dosage necessitated by the patient's age or the technical difficulties of intravenous medication the same outline of treatment as in adults may be followed. The two types of involvement responsible for most of the therapeutic difficulties of late acquired syphilis, cardiovascular and neurosyphilis, are less troublesome in the late congenital form. For an unknown reason cardiovascular lesions occur with such rarity in late congenital syphilis that they may be dismissed as practically nonexistent. Neurosyphilis of various clinical types occurs slightly less frequently in late congenital (about 15 per cent) than in late acquired syphilis (about 25 per cent). *Asymptomatic neurosyphilis is found in about 10 per cent of congenital syphilitics over the age of five.* Most neurosyphilitic children die young. Excepting those individuals with obvious clinical evidence of neuraxis involvement, the therapeutic problem in late congenital syphilis is essentially identical with that in latent and benign late acquired syphilis.

Mapharsen should be the arsenical drug of choice when intravenous medication is technically easy; otherwise (in children under the age of 6 but not in older children—see Chapter VII) sulpharsphenamine may be used as in infants. Below the age of 15 the dosage of mapharsen should be on the basis of weight (1 mgm/kg.). In older children, adult dosage may be employed. Bismuth is preferable to mercury in older children. Depending on whether or not the infection is latent or is accompanied by active lesions, an essentially similar plan as to character and duration of treatment may be followed as is suggested for latent and benign late syphilis in Chapters XVI and XVII.

The relationship of late congenital syphilis to the infantile infection and its treatment.—In the following sections are summarized the data secured by Smith in 267 patients with late congenital syphilis from our own clinic, each followed for 2 years or longer.

In the vast majority of our patients with late congenital syphilis (89 per cent) no history could be obtained of such infantile lesions as snuffles, skin eruptions, etc. Only 2 per cent of the total number had ever received any treatment for syphilis as infants. These facts suggest, first, that the

lesions of late congenital syphilis tend particularly to appear in those patients in whom early infantile lesions were absent or insignificant (a parallel situation with the acquired infection in adults) and second that treatment for infantile syphilis may be successful in preventing the development of late lesions in a high proportion of cases

The results of treatment in late congenital syphilis —For purposes of comparison with early congenital syphilis Jeans and Cooke s summary of treatment results in late congenital syphilis (in children over one year of age) is shown in Table 113 According to their definition "cure" consists of freedom from clinical and serological syphilis for at least three years. Obviously much more treatment is necessary in late than in early congenital syphilis to accomplish equivalent results

TABLE 113
THE RESULTS OF TREATMENT IN LATE CONGENITAL SYPHILIS
(Jeans and Cooke)

Duration of treatment	Total children	During subsequent observation period of at least 3 years, per cent	
		"Cured	Not "cured"
6–12 months	66	12 1	87 9†
More than 1 year	193	44 0‡	56 0§

Including 1 child with known neurosyphilis.
† Including 7 children with known neurosyphilis.
‡ Including 14 children with known neurosyphilis.
§ Including 20 children with known neurosyphilis.

The study of our own material by Smith permits a number of statements as to factors influencing the ultimate outcome of treatment None of Smith's patients was observed for less than 2 years, and most of them for much longer periods of time As in late acquired syphilis, the ultimate outcome is expressed largely in clinical terms the result is considered to be satisfactory if lesions originally present disappeared and there was no evidence of subsequent progression or relapse or in the case of patients with irremediable stigmata or scars (e g saddle nose dental abnormalities, sabre shins, deafness corneal scarring) if no fresh active lesions developed during the observation period the patient s general health remaining as good as or better than on admission

The attempt to correlate the clinical outcome with duration of treatment provides the data shown in Table 114 Three treatment groups are considered, corresponding closely to the three time periods —treatment for less than 6 months, from 6–12 months and for more than one year So far as the maintenance of good health is concerned two facts stand out clearly First, in contrast to late acquired syphilis of all types there is no direct relationship of clinical outcome with the total duration of treatment A relatively small amount of treatment accomplishes as much in preventing subsequent relapse or progression as a great deal. Second like

TABLE 114

RELATIONSHIP OF DURATION OF TREATMENT TO CLINICAL OUTCOME IN LATE CONGENITAL SYPHILIS

Status of disease on admission	Per cent of patients with satisfactory clinical outcome when treatment was		
	Less than 30 weeks	30–50 weeks	More than 50 weeks
Active lesions present	6.6	77.1	83.1
Latent	95.0	80.0	92.3

the course of events in late acquired syphilis, the presence of active lesions of any type before treatment predisposes to subsequent relapse, which is far less common when the patient has attained spontaneous latency.* The patient's own defense mechanism, therefore, plays as important a rôle in congenital as in acquired syphilis.

There is no evidence in our own material that involvement of any particular organ or system (except the nervous system) predisposes to relapse or progression, which occurs with equal frequency whether the original lesion involves eye, ear, bones or other organs. The most frequently observed relapse is of course interstitial keratitis, which accounts for nearly half the observed instances.

White patients are definitely less amenable to treatment than Negroes. In Smith's material, relapse or progression occurred in 25 per cent of white children and in only 15 per cent of the Negroes. The difference represents almost entirely the much higher incidence of congenital neurosyphilis among whites. Although in late congenital as in late acquired syphilis, Negroes are less susceptible to neurosyphilis than whites, the sex differences observed in the acquired infection are not present in the congenital type. Neurosyphilis is equally common among male and female congenital syphilitics, and there is no evidence that sex exercises any influence in the outcome of treatment in the congenital disease. The age of the patient at the time of starting treatment has no influence on the ultimate result, which is as satisfactory when treatment is begun in late adolescence or early adult life as in early childhood.

In an earlier chapter we have presented evidence to show that in acquired latent syphilis (but not in other types) the ultimate clinical outcome is improved upon by the passage of time. This appears not to be true in late congenital syphilis, as indicated in Table 115, though in this group of patients the material is too small to permit division into the categories of latency and of patients with active lesions. Incidentally, this table gives some idea of the adequacy of the observation period in our material: 60 patients have been followed for more than 11 years.

* Included in the category of latency are patients with or without the basic stigmata of congenital syphilis in whom the only evidence of clinical activity is the presence of a positive blood serologic test. A few of these patients had had active lesions, usually interstitial keratitis, in years past, but in all spontaneous healing had occurred and there were no active lesions when treatment was started.

TABLE 115

THE RELATIONSHIP OF DURATION OF OBSERVATION TO ULTIMATE CLINICAL OUTCOME IN LATE CONGENITAL SYPHILIS (AFTER F R. SMITH, JR.)

Duration of observation	Total patients	Per cent with satisfactory clinical outcome
2-5 years	107	77 5
6-10 years	100	80 0
11-20 years	60	80 0

The relationship of duration of treatment to serologic reversal in our patients provides a surprise. The data, shown in Table 116 indicate that a year of treatment accomplishes about as much toward this end as larger amounts and that with treatment of any duration seroresistance (Wassermann fastness) may be expected in about half the patients treated. Furthermore there is no correlation between serologic response and type of lesion. Seroresistance is equally common in late congenital syphilis whether the infection is latent or whether the involvement is osseous, ocular or in other structures.

TABLE 116

THE BLOOD WASSERMANN RESPONSE TO TREATMENT IN LATE CONGENITAL SYPHILIS (AFTER F R. SMITH, JR.)

Duration of treatment	Total patients	Wassermann response to treatment, per cent		
		Always negative	Always positive	Reversed to negative
Less than 1 year	172	8 7	50 5	40 7
More than 1 year	95	2 1	50 5	47 3

It is important to determine whether in late congenital syphilis persistent serologic positivity is of more serious significance from the standpoint of clinical relapse or progression, than it appears to be in late acquired syphilis This point is examined in Table 117 It seems clear that

TABLE 117

THE RELATIONSHIP OF SERORESISTANCE TO ULTIMATE CLINICAL OUTCOME IN LATE CONGENITAL SYPHILIS (AFTER F R. SMITH, JR.)

Blood Wassermann	Total patients	Percentage with	
		Ultimate clinical outcome satisfactory	Clinical progression or relapse
Fast	162	77 7	21 5
Not fast	105	80 0	20 0

serologic reversal or its absence as a result of treatment has no important bearing on clinical progress clinical relapse or progression occurs as often in one set of circumstances as in the other It is entirely probable therefore that in late congenital as in late acquired syphilis the high incidence of seroresistance (higher in Smith's series than in many other similar reports) after large amounts of treatment is an expression not of the inadequacy of treatment, but of the increased delicacy of modern serologic technique.

To summarize Smith's observations it appears that in late congenital syphilis, the ultimate clinical and serologic outcome of treatment is equally satisfactory after 6–12 months of treatment as after a larger amount that the prognosis is better in patients who have achieved spontaneous latency than in those with active lesions before treatment that the results of treatment are better in Negroes than whites (because of the lower incidence of neurosyphilis among Negro congenital syphilitics) that neither sex nor age at starting treatment plays any part in the out come that the results of treatment are not improved upon by the passage of time and that seroresistance is not of serious prognostic import.

The treatment of special types of congenital syphilis Latent congenital syphilis —In latent late congenital syphilis the whole justification for treatment lies in the possibility of preventing the future development of active lesions Potential infectiousness a factor requiring consideration in latent acquired syphilis, may be dismissed as unimportant in the congenital infection It is customary to tell the patient with late congenital syphilis (or his parents) that treatment must be given to prevent the probable future development of two lesions in particular interstitial keratitis and nerve deafness the occurrence of either one of which may seriously handicap or even incapacitate the child. This statement appears to be justified by Smith's study which shows that permanent latency (i.e. the absence of late lesions of any type) is less common in congenital than in acquired syphilis the incidence of latency diminishes steadily in successively older age groups. Thus the congenital syphilitic if untreated is more likely to develop some lesion at some time than the patient with the acquired infection. What evidence have we that these relapses may be prevented by treatment during the stage of latency? It is suggestive but not conclusive that in Smith's series only 4 of 115 treated patients with latent congenital syphilis developed relapsing active lesions (2 osseous 2 ocular) This is not necessarily evidence that treatment has prevented relapse It is possible though hardly likely in view of the high incidence of lesions in untreated congenital syphilis, that the patient's own defense mechanism might have enabled him to do as well if he had not been treated.

A second method of approach is to examine the age incidence at onset in previously untreated patients of the two most frequent relapsing lesions interstitial keratitis and nerve deafness and to compare this with the age at the time of starting treatment of latent congenital syphilitics. If it appears that the average patient with latency is diagnosed and started on treatment at a significantly earlier age than that at which he

might be expected to develop these two lesions if untreated, and if in turn these lesions do not then appear the conclusion that treatment has played a part in preventing them appears to be justified. This is actually the case. The age at onset of interstitial keratitis and nerve deafness in a large series of patients (gathered from Smith Jeans and Cooke, Igersheimer and Alexander) is shown in Fig. 84 * The mean age at onset of interstitial keratitis is 11.8 years of nerve deafness 16.9 years and a signifi-

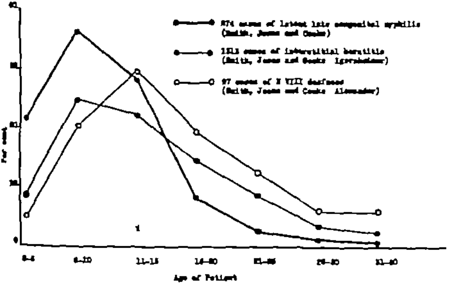


FIG. 84.—Showing the age at which interstitial keratitis (1,313 patients) and nerve deafness (97 patients) appeared in previously untreated patients, as compared with the age at the start of treatment of 574 patients with latent congenital syphilis. These curves indicate that treatment was begun, in these patients with latent congenital syphilis, at an average age significantly before that at which lesions might have been expected to develop; since such lesions did not develop, treatment played a part in preventing them.

cantly large number of patients develop one or both of these lesions after the age of 20 Contrasted with these is the curve of the ages *at the start of treatment* of 574 patients with latent congenital syphilis (Smith Jeans and Cooke) The majority of such patients in these two series were started on treatment *before* the usual time at which ocular or auditory lesions might have been expected to appear (i.e. before the age of 15) these lesions did not develop It is therefore probable that treatment was at least in part successful in preventing their appearance.

The patient with latent congenital syphilis should be treated for a minimum period of one year

The treatment of interstitial keratitis —This subject is discussed in detail in Chapter XX Here it is necessary to add on the basis of Smith's study that to obtain the best results from the twin standpoints

* The data as to the age incidence of interstitial keratitis are confirmed by the more recent study of Klauder and Vandoren. (Chapter XXI)

of healing of the acute lesion and resolution of its scar, and of prevention of subsequent relapse treatment should be continuous and prolonged to a minimum of two years

Prompted by Sydenstricker's reports we have recently treated several children suffering from interstitial keratitis with riboflavine either as an adjunct to or substitute for routine antisyphilitic treatment. It is too soon as yet to evaluate the results of this study but thus far they are not encouraging.

The treatment of nerve deafness —Reference has already been made to this topic in Chapter XXIV Smith s study of our material has provided one important point with reference to diagnosis namely that in 64 congenital syphilitics with nerve deafness there was associated clinical evidence of neurosyphilis in only one and the spinal fluid was normal in 31 of the 33 patients tested Almost surely therefore the lesion in late congenital syphilis is located outside the nervous system and most probably in the end organ of the inner ear itself (Ciocco and Weinstein Mayer and Fraser)

As to treatment results few of the patients in Smith s series were studied by audiometric methods but even on the basis of the patient s own statements the opinion is confirmed that the prognosis for the restoration of hearing is relatively hopeless Only 9 5 per cent of patients reported any benefit from treatment 74 5 per cent were unimproved and 16 per cent were worse.

Imbecility and congenital syphilis —This subject has been studied by Menninger Dayton and Jenkins among others. The relationship of congenital syphilis to feeblemindedness is not entirely clear it is probable that in many if not in most instances the mental defect is based on other causes. At any rate there is general agreement that antisyphilitic treatment has little or no beneficial effect on the mental deterioration.

Congenital neurosyphilis —The prognosis of asymptomatic neurosyphilis seems on the basis of Jeans and Cooke s studies as well as our own to be about the same as in the acquired disease. After the development of clinical signs (especially juvenile paresis) however the outlook is much worse in congenital than in acquired neurosyphilis The methods of treatment are identical with those outlined in Chapter XXIV with the exception of the use of tryparsamide This drug should never be used in infants or in children too young to give an accurate account of subjective visual sensations The risk of blindness is too great.

Fever therapy especially malaria is beginning to be widely used in juvenile neurosyphilitics especially paretics We have employed it in 20 cases with good results except in those children who had already deteriorated before the onset of treatment. In general, our feeling is that malaria should be employed at some stage of treatment in every juvenile neurosyphilitic whose spinal fluid abnormalities are resistant to standard methods and at the start of treatment in patients with obvious juvenile paresis. The problem of treatment of congenital neurosyphilis and especially juvenile paresis is considered in great detail in the excellent monograph by Menninger

Acetarsone in the treatment of congenital syphilis.—During the past fifteen years numerous articles have appeared in the German French, and American literature describing the results of treatment of congenital syphilis with acetarsone (stovarsol) given by mouth. The best of the recent reports in this country is that of Pillsbury and Perlman who describe the results of treatment with acetarsone in 187 carefully studied syphilitic infants and children. These authors report an incidence of toxic reactions in 11 per cent of their patients, in more than a third of whom evidences of nephritis were found. Toxic manifestations were much more frequent in hospitalized infants to whom the drug was given under close supervision than in children treated on an ambulatory basis This suggested to Pillsbury and Perlman the obvious explanation that when the administration of acetarsone is entrusted to parents or relatives it is often used in inadequate dosage or even not at all

Pillsbury and Perlman used the plan of Maxwell and Glaser by which the infant receives 14 grams of acetarsone in a forty-nine-day course, approximately twice as much acetarsone as that recommended by Bratusch-Marrain. Because of the high incidence of toxic reactions with the less conservative method of treatment, they prefer the plan devised by Bratusch-Marrain in which the dosage is based upon the weight of the child as follows

First week	0 005	gram per kilogram daily
Second week	0 01	gram per kilogram daily
Third week	0 015	gram per kilogram daily
Next six weeks	0 02	gram per kilogram daily

The amount of acetarsone in grams consumed during one nine-week course by this system corresponds approximately to the weight of the infant in kilograms. This course of treatment is followed by a rest period of four to six weeks and then the course of treatment is repeated until the serologic test taken after every course, is negative three times in succession An additional safety course" given six months after the cessation of the regular course is recommended.

Although the incidence of reactions in our smaller series of less closely observed patients is lower than in the Pillsbury and Perlman series, we agree with their conclusions that the effect of acetarsone in arresting congenital syphilis is inferior to that of other arsenical and bismuth preparations, and that its use is generally inadvisable since it cannot be controlled by experimental studies of spirochetícidal action and toxicity in animals and since administration to outpatients is not assured. In general, we feel that the same major objection applies to acetarsone as to any other oral method of treatment of syphilis —it is useful only in highly intelligent and highly cooperative patients since many syphilitic patients do not qualify in these respects Its usefulness is sharply limited.

The marriage of congenital syphilitics Third generation syphilis.—Smith and Howard of our clinic reviewed this subject in our own material. A male with congenital syphilis whether treated or untreated, may marry with complete safety to wife and future offspring. A female

Chapter XXVIII

THE INTERPRETATION OF SEROLOGIC TESTS IN THE DIAGNOSIS AND TREATMENT OF SYPHILIS THE PROVOCATIVE TEST SERORESISTANCE

The importance of serologic tests as an aid in the diagnosis and treatment of syphilis can hardly be over-estimated Common sense in their use and interpretation is equally essential. To delay treatment of a patient with a darkfield positive lesion until the return of a serologic report is indefensible while in the absence of definite history of infection or clinical signs treatment should never be started on the basis of a single unsupported positive test, because of the danger of laboratory error To prolong treatment over a period of many years in the hope of reversing an irreducibly fixed positive test to negative is in many instances both unnecessary and unwise. It is the clear duty of the physician to correlate the laboratory report with the history and clinical findings in arriving at a conclusion as to the presence or absence of syphilitic infection or as to the significance of the test in a patient under treatment. In this however he is frequently handicapped by his ignorance of the numerous sources of error inherent in the several complement-fixation (Wassermann) or flocculation techniques and by conflicting views as to the significance of the serologic findings. The present chapter therefore presents a brief discussion of the use and the value of the complement-fixation and precipitation tests in diagnosis and treatment. The technique of these reactions will not be described save insofar as it affects their interpretation by the physician.

The Nature of the Serum Change in Syphilis

In the course of syphilitic infection, *a substance appears in the serum* which has the physical and chemical properties of an antibody Whether this substance is actually an antibody to *T pallidum* will not be definitely known until it has been possible to cultivate the pathogenic organism. The diagnostic tests for syphilis in current use rest on the fact that this antibody like globulin termed *reagin* has the peculiar property *as yet not* adequately explained of combining with finely divided particles of mammalian tissue lipoids. As a result of that combination the lipoidal particles clump together to form visible aggregates and that aggregation is used as the diagnostic criterion in the various flocculation tests for syphilis (Eagle Hinton Kahn Kline) Moreover after combining with reagin, the lipoidal particles are able to bind ('fix) complement and that phenomenon underlies the complement fixation (Wassermann) test for syphilis. There are thus in current use only two types of diagnostic test, flocculation and complement fixation both of which rest on the fact that syphilitic serum reacts with suspensions of tissue lipoids (antigen") as if it contained an antibody to those lipoids.

Positive, Doubtful and Negative Reactions Definition

Positive reactions —A positive report, whether in a Wassermann test or any of the numerous flocculation tests implies that in the opinion of the technician there was no doubt as to the abnormal result. In the case of the Wassermann reaction it implies that neither the patient's serum nor the antigen alone destroyed complement, but that a combination of the two fixed complement so completely that sensitized red cells showed no demonstrable lysis after one-half hour incubation at 37°C In the flocculation tests it implies that the serum in question caused indubitable aggregation of a suspension of tissue lipoid particles, while control normal sera tested simultaneously had no such effect.

Doubtful reactions —A doubtful report implies that the result of the test, although suggestive was not sufficiently clear-cut to justify a definite report of positive. In the Wassermann test the cells were partially dissolved, in the several flocculation tests, the lipoidal particle showed only partial and dubious clumping

It should be pointed out that this doubtful category includes all results which were formerly reported as plus-minus one plus, or "two plus" while the report of 'positive' embraces results formerly reported as "three plus and 'four plus. The reason for discarding the latter 'plus" classification will be discussed in the section on quantitative tests.

Negative results —A report of negative indicates that there was no demonstrable aggregation of lipoid in the flocculation tests or that the cells were completely dissolved in the Wassermann test.

Various Types of False Positive or False Doubtful Reactions

If syphilis were the only condition which causes serum to react with mammalian tissue lipoids, and if there were no other qualifications to a report of positive then every person giving such a reaction could automatically be diagnosed as syphilitic. This however is far from the case. It is essential that the physician learn to appraise the result of the laboratory report not with suspicion, but with due cognizance of the many factors other than syphilis which may conspire to cause a false positive or false doubtful reaction.

Technical error —First and foremost is a mistake in the actual performance of the test. The frequency with which such technical false reactions occur is conditioned in part by the reliability of the technician and by the type of test performed. The complexity of the Wassermann reaction is too well known to require discussion and the danger of false positive reactions due to some technical maladjustment of the reagents is quite real. Moreover contrary to general belief and despite their apparent technical simplicity the flocculation tests also provide numerous pitfalls for the unwary and inexperienced worker particularly in the reading of results This can be readily demonstrated by having different technicians carry out series of tests on the same group of syphilitic sera with presumably the same flocculation technique The discrepancies obtained

will give pause both to those who regard these tests as far simpler and more reliable than the Wassermann reaction, and to those who accept the laboratory report uncritically assuming it to be the result of an objective and impersonal examination. Technical errors usually cause incomplete hemolysis, or partial aggregation, that is false doubtful results rather than outspoken false positive results. The latter however, do occur

A single positive or doubtful report, no matter by what technique, should therefore never be accepted at its face value in the absence of indubitable clinical findings until the same result is obtained upon the examination of a second specimen or of the same specimen in a second laboratory The harm done by a mistaken diagnosis of syphilis based on a false laboratory report is frequently irreparable and may outweigh any number of false negative reports.

The possibility of a mistaken diagnosis of syphilis due to laboratory error has in recent years been greatly increased by the use of "exclusion "presumptive and "screen tests These are simplified flocculation tests which have been deliberately increased in sensitivity to the point that the highly unstable lipoidal suspension shows some aggregation even in normal sera. The incidence of such false positive or false doubtful reactions may vary from less than 1 to more than 10 per cent in the hands of different workers. A negative "screen test may therefore be taken at its face value since the less sensitive but strictly specific, diagnostic test would in all probability also have been negative A positive or doubtful screen test however should never be reported to the physician unless at least one and preferably two strictly specific diagnostic tests on the same specimen are similarly positive or doubtful. Conversely the physician should ignore a positive or doubtful screen test obtained in a patient not known to have syphilis unless at least one and preferably two confirmatory tests with strictly specific techniques are likewise positive or doubtful.

In general and screen tests excluded a reliable laboratory should obtain not more than one false doubtful or positive result in every 100 specimens examined The physician in choosing the laboratory to which he will submit blood specimens for serologic examination should consider the following factors 1) The technique used should be one which has been officially evaluated by the United States Public Health Service and the American Society of Clinical Pathologists and found to give satisfactory results in the hands of competent workers *The Eagle Hinton Kahn*, and Kline flocculation techniques the Eagle Kolmer and New York State Wassermann techniques and a few others have been so evaluated. 2) If the laboratory is a State Health Department laboratory it should have given satisfactory performances in the last few annual serologic evaluation studies conducted by the United States Public Health Service. A laboratory is approved as satisfactory if it has a sensitivity in syphilitic patients within 10 per cent of that obtained by the same technique in the hands of an expert serologist and a specificity in non-syphilitic patients of 99 per cent or more (1 per cent or less false positive reactions) 3) If the laboratory is not a State Health Department laboratory it should have been officially approved by the latter or by some equivalent agency for

the particular technique employed. If there is no machinery for such official certification the equipment and personnel should be such as to justify the belief that the tests will be done accurately in accordance with the published directions.

Biologic false positive reactions due to disease other than syphilis.—In the decade immediately following the development of the Wassermann test, all sorts of conditions and diseases were reported to cause positive reactions in the absence of syphilitic infection. Many of these early reports have been shown by subsequent studies to be in error. *Technical error excluded*, icebox incubation and the use of cholesterolized antigens do not cause false positive Wassermann tests. Similarly there is no satisfactory evidence that pregnancy, diabetes, menstruation or ether anesthesia cause the appearance of positive serodiagnostic tests in the absence of syphilitic infection.

At the other extreme, and despite a large and conflicting literature, it seems clearly established by recent studies that both leprosy and malaria cause false positive reactions. The incidence of these is estimated to be as high as 50–70 per cent in some forms of nodular leprosy (Cumming and his co-workers), while the majority of malarial patients are said to become seropositive, even if only temporarily, at some stage of the acute infection (Hazen and his associates, Kitchen, Webb and Kupper). In-

CONDITIONS FREQUENTLY RESPONSIBLE FOR BIOLOGIC FALSE POSITIVE SEROLOGIC TESTS FOR SYPHILIS

1. Infectious mononucleosis
2. Malaria
3. Yaws
4. Leprosy
5. Upper respiratory infections
6. Vaccinia
7. Serum treatment (?)

FIG. 85

fectious mononucleosis causes positive Wassermann or flocculation tests (usually the former) in approximately 20 per cent of the cases (Bernstein).* Yaws, caused by an organism morphologically indistinguishable from *T. pallidum*, has been found to give positive serum tests as regularly as does syphilis. Upper respiratory infections of various types and vaccinia cause biologic false positive tests in an as yet undetermined proportion of cases. Serum treatment of one or another sort may produce the same result.

* The particular importance of this lies in the fact that infectious mononucleosis is gradually being recognized as a widespread, extremely common disease, with typical symptoms often trivial or even wholly lacking.

Between these two groups of diseases lies a third group concerning which the evidence even now is inconclusive. That false reactions occur with considerable frequency in the course of rat-bite fever lymphocytic chorio-meningitis trypanosomiasis and relapsing fever seems probable, although the number of published cases is too few to justify definite conclusions That false reactions are caused in some cases with active tuberculosis and that such false reactions are usually weak, doubtful in character is indicated by several recent studies (Cumming and others Parran and Emerson) Finally the data with respect to jaundice hyperpyrexia, and acute infections in general are so conflicting as to necessitate a careful re-study A few cases adequately controlled with negative tests before the onset of an acute infection positive tests for a variable period of time followed by permanent seronegativity following the subsidence of the infectious process would be of more value than several hundred cases tested at random with no adequate control for the possible presence of latent syphilis (Mohr Moore and Eagle)

False positive or doubtful reactions occurring in normal individuals —It seems fairly clear that the incidence of positive or doubtful tests in clinically normal non-syphilitic persons is so small (perhaps as great as 1 in 1 000 perhaps less than 1 in 4 000—Eagle) that considered only as a public health problem, it is justifiable to treat all such confirmed seropositive reactors for syphilis On the other hand it seems equally clear (Mohr Moore and Eagle) that in the rare case actually non-syphilitic persons may give false positive tests. Characteristically these false reactions tend to be weak, the laboratory report often being doubtful rather than positive and the results obtained with two or more different tests tend to be conflicting. The diagnostic problem presented by such serologic reports in individuals with no other evidence of syphilis is discussed in the following sections. The reports (Barnett Jones and Kulchar Sherwood, Bond and Canuteson) that normal serum frequently contains reagin in quantities too small however to affect the diagnostic test, are as yet too conflicting to be accepted as established fact. The false positive reactions observed in the non-syphilitic newborn child due to the placental transfer of reagin from a syphilitic and seropositive mother are discussed in Chapter XXVI and in a following section of this Chapter

The Interpretation of the Laboratory Test in the Diagnosis of Syphilis

What construction should be placed by the physician on a report of *positive* in a person who presents no clinical evidence of syphilitic infection? It is assumed that laboratory error has been excluded by a confirmatory test on a second specimen and that the test in question is one which has proved consistently reliable in the past. It is assumed further that the patient is not suffering from some acute non-syphilitic disease which might conceivably cause a false positive test in such case serologic follow-up is indicated for as long a time as is necessary to establish the fact that the positive or doubtful tests were not due to the intercurrent infection

It goes without saying that any patient giving confirmed positive tests

for syphilis must be thoroughly investigated from the point of view of syphilitic infection that investigation to include a careful history serologic and clinical examination of possible contacts (including the immediate family) and a complete physical examination, with particular emphasis on the heart and central nervous system and including spinal puncture. Even if these supply no additional information the well known tendency of syphilitic infection to remain latent, clinically submerged, for long periods of time and the rareness with which normal persons give false positive tests for syphilis alike enjoin the diagnosis of latent syphilis and appropriate treatment in the great majority of cases.

In the exceptional case however the physician is justified in treating even a confirmed positive or doubtful serologic test with skepticism, and in reserving judgment until he has been able to procure additional information. No hard and fast rules can be laid down, but the following types of cases (all of which have actually been encountered in clinical practice of Mohr Moore and Eagle) should cause suspicion. In all of these it will be taken for granted that the patient presents no clinical evidence or history of syphilitic infection

1 Female patients, found to be virgin who give no history of what may have been an extragenital chancre. The physician may have reason to believe an occasional male patient who also denies sexual exposure.

2. Patients, whom the physician has reason to believe truthful who in the past have had one or more negative tests with an equally sensitive technique, and who deny any exposure in the interim

3 Married patients who since marriage have had one or more negative tests preceding the positive result and whose marital partner despite unrestricted intercourse, is still seronegative.

4. Persons not sexually promiscuous in whom tests with different techniques, or with the same technique in different laboratories or on different occasions, give conflicting results. With the increasing sensitivity of some laboratory tests more and more patients are falling into this category and it constitutes perhaps the most important diagnostic problem in syphilis today It is essential for the physician to recognize that a laboratory report in which an exclusion 'presumptive or 'screen test is positive, while a diagnostic test is negative, does not constitute a diagnostic problem in a patient who presents no clinical evidence or history of syphilitic infection. These "screening procedures are deliberately designed to be hypersensitive and are known to give technical false positive tests which reflect the instability of the antigen rather than a biologic property of the serum. Indeed, such reports should not be sent to the physician in the first place. Even with the screen tests excluded, however there remains a considerable residue of patients who consistently give conflicting serologic tests, and their disposition is a problem of the first magnitude

What to do about persons similar to those illustrated in the foregoing case reports is a question to which no *ex cathedra* answer is now possible. On the basis of our present knowledge the following suggestions have been made by Moore Eagle and Mohr

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identifying as non-syphilitic some of these patients who give confusing serologic findings. The use of wholly non-specific antigens such as those prepared from bacteria, milk, or egg lecithin will identify the rare serum which reacts positively to all complement-fixation tests. One such case has been recently reported (Mohr, Moore and Eagle) and we have observed others.

The interpretation of the doubtful result in the diagnosis of syphilis —Everything said in the foregoing section concerning the positive report applies with equal force to the doubtful test. Granted that laboratory errors when they do occur usually take the form of false doubtful results the converse is not true. All doubtful reports are not false. The large majority of doubtful results obtained in a good laboratory reflect the presence of small but definite quantities of reagin and actual syphilitic infection often though not always previously treated.

Where the diagnosis of syphilis rests solely upon a doubtful laboratory report, or where this result serves to confirm suspicions aroused by some clinical findings, such a test should be repeated not once, but several times. If the original doubtful report was due to the actual presence of reagin in the serum, one or more subsequent tests are frequently positive. Check specimens to another laboratory or by another type of test, frequently serve to verify the suspicions aroused by the first report. Thus a series of bi-weekly tests reported as doubtful, positive positive, doubtful, from a reliable laboratory can only mean that the serum of the patient contains small but definite quantities of reagin. On the other hand a series such as doubtful negative negative negative usually means that the original report was in error

The reservations made in the foregoing section to the interpretation of positive results apply with even greater force to a confirmed *doubtful* result.

The negative report in the diagnosis of syphilis —The extraordinary specificity of the various serologic tests for syphilis goes hand in hand with marked sensitivity Thus, an analysis of the results at the Johns Hopkins Hospital indicates that 85–90 per cent of individuals with clinically active syphilis, seen in the years 1920–1930 including all manifestations of the disease, were seropositive when tested by an icebox Wassermann technique at the time of the first examination. The test employed *has since been made more sensitive, and there is reason to believe* that with the Wassermann and flocculation techniques now in use, the proportion detected is 90–95 per cent. Nevertheless statistics are meaningless in the individual case and a persistently negative serologic test, even by the most sensitive technique available, does not exclude syphilitic infection. Even secondary syphilis and general paresis frequently stated to be seropositive in 100 per cent of the cases, in the rare case give persistently negative serum reactions. In the presence of highly suspicious clinical manifestations therefore a negative serum reaction, although suggestive, cannot be accepted as absolute proof of the absence of syphilitic infection. In particular is this true of suspected late congenital syphilis or of neurosyphilis.

Quantitative Serologic Tests The Serologic Diagnosis of Congenital Syphilis

Reagin titre —As in the analogous case of the Widal reaction syphilitic serum may contain many times the amount of reagin necessary to give a positive result. As with any other agglutination precipitation or complement fixation reaction the degree of positivity may be and usually is, expressed as the highest dilution in which the serum is still positive Titres of 200 are not uncommon and titres of 3200 have actually been observed. It is obvious that the continued use of the terms one plus' two plus three plus' and four plus to characterize supposed degrees of positivity is an anachronism which cannot be too strongly discouraged Ostensibly the term four plus applies to completely" ('strongly') positive reactions while 'three plus ' two plus and one plus represent decreasing degrees of positivity In the Wassermann reaction these terms signify intermediate degrees of hemolysis interpolated between four plus' (no hemolysis) and 0 (complete hemolysis) in the various flocculation reactions their distinction is even more vague representing degrees of aggregation intermediate between four plus' (definite and marked clumping of lipoid particles) and 0 (no detectable aggregation)

Actually however the term 'four plus does not mean completely' or "strongly' positive and the terms one plus two plus 'three plus' cover so minute and insignificant a portion of the entire range of positivity as to be devoid of quantitative significance By definition the term "four plus applies to any serum containing enough reagin to cause complement fixation or precipitation whether that serum contains one or 800 times that minimal fixing or precipitating quantity Just as clearly the terms one two and three plus upon which so much stress has been laid as a measure of positivity cover a minute portion of the entire range of variation the region of least reagin content and the difference between them is so insignificant that the same serum tested in duplicate on the same day by the same individual may yield a one, two or three plus" result due solely to slight differences in the measurement of reagents

It follows that the refined methods which have been suggested for measuring degrees of partial hemolysis in the Wassermann reaction or degrees of partial aggregation in the flocculation test serve no useful purpose. Any test which is not clearly positive (no hemolysis definite precipitation the solid black section of Fig 87) is and should be reported as *doubtful*, this term to include all plus-minus one plus and 'two plus" reactions (the cross-hatched section of Fig 87)

The use of quantitative serum tests —To obtain a titre of a "positive serum necessitates carrying out the flocculation or complement fixation reactions on serial dilutions of serum and clearly multiplies the work of the laboratory In the great majority of cases, the information so obtained is of no practical significance and does not justify the additional laboratory work involved A patient whose serum has a reagin titre of 1 (barely positive in whole serum) is no less syphilitic than one with a titre of 1000 (serum positive up to a 1 1000 dilution) *There is no good*

evidence that the reagin titre is in any sense a measure of the extent or activity of the syphilitic process. All possible variations in titre are encountered in every type of syphilitic involvement and although the average titre may be lower in latent syphilis and in tabes than it is in paresis or cardiovas-

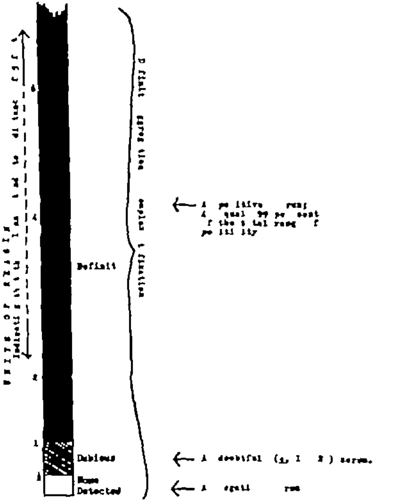


FIG. 67 —Illustrating the extremely small range of "positivity" occupied by the "doubtful (± 1+ 2+) Wassermann or flocculation test.

cular syphilis (Moore and Eagle) the degree of variation encountered is so large as to render the absolute titre of no significance in the individual patient

The quantitative titre is of some value in following the serologic response to treatment (pp 84 279) It is of considerable value in evaluating the significance of a positive serum test in the clinically normal newborn

child of a syphilitic mother The physician in such a case is faced with the decision as to whether this serum reagin is due merely to the placental transfer of reagin from a syphilitic seropositive mother to a normal child or whether the positive cord blood reaction reflects the presence of congenital syphilis, as yet latent. The correct procedure in such cases is to supplement a thorough clinical study and careful follow up with repeated quantitative serologic tests If the titre of the serum test falls

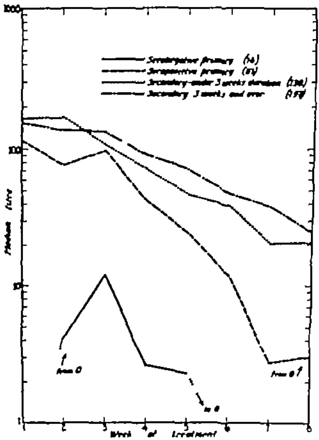


FIG. 83.—The quantitative fall of serum reagin in patients with various types of early syphilis during the first course of arsenical treatment (Crosby and Campbell) Note the absence of provocative rise in all patients except those with seronegative primary syphilis (see p 535).

progressively over the first 2 or 3 months of life eventually becoming and remaining negative (see Fig 82) and if the child still presents no clinical evidence of congenital syphilis then the initial positive tests may be safely ascribed to the placental transfer of reagin. If however the titre rises continuously or if after an initial fall it once again rises to a comparatively high level (see Fig 83) the child probably has congenital syphilis In such cases the rising titre is usually accompanied or soon followed by obvious clinical manifestations.

In evaluating the weekly or bi-weekly progress of the serum titre of a patient under treatment or observation, the limitations of the quantitative technique must be borne in mind The sensitivity of the Wassermann test, even in a good laboratory may vary by as much as 50 to 100 per cent from week to week, and changes in the apparent titre of that order of magnitude or less must accordingly be regarded with skepticism unless a series of such tests shows a definite trend. The flocculation test is far more constant in its day to day sensitivity and apparent changes in flocculation titre are more likely to reflect an actual change in the serum reagin content.

Multiple Tests Conflicting Serologic Tests

The intra-laboratory check of the Wassermann reaction by one of the flocculation techniques or the use of several flocculation tests serves several purposes. A maximum number of sera are thereby detected for in any large series of tests there are always some sera which paradoxically react only with an ordinarily less sensitive technique. The use of multiple tests is, further a recognition of human fallibility and of the manifold possibilities of technical error inherent in any technique. Finally the value of a positive result to the physician is considerably enhanced if two or more techniques have been simultaneously found to be positive or doubtful.

On the other hand the use of more than one test has a serious drawback. Necessarily the more tests used, the larger will be the proportion of sera which give conflicting results and which accordingly present a diagnostic problem to the physician. In recognition of this difficulty many laboratories have attempted to minimize the number of conflicting reports by one of several procedures. The use of an "antigen battery" in the Wassermann test i.e., the use of antigens of low intermediate, and high sensitivity has been recognized as an outmoded procedure which should be discarded. Only too often the physician has been unnecessarily confused by a report that in a given serum the test is e.g. negative with a plain alcoholic antigen but positive with a cholesterolised antigen. This type of report has no significance other than that the plain alcoholic extract is comparatively insensitive. Each laboratory should select and employ routinely a single antigen which in its opinion gives maximum sensitivity and specificity combined with relative freedom from technical false positive reactions.

In the second place, many laboratories which use a simplified supersensitive "screen" test now report the result of that test to the physician only if it is negative. If the result of the preliminary "screen' procedure is positive or doubtful the serum is re-tested with one or more confirmatory techniques known to be strictly specific and only the result of that confirmatory test is made known to the physician whether it be positive doubtful or negative. A large number of conflicting reports which all too often have led to the mistaken diagnosis of syphilis are thus eliminated nor has the physician been deprived of any significant information for an unsupported positive screen test is of no diagnostic import

Finally in some laboratories which carry out three or four different

tests on every specimen the burden of interpreting conflicting reports has been somewhat simplified for the physician by the fact that, instead of reporting the results of the individual techniques the laboratory sends an over-all report of positive doubtful or negative

We have so far considered only conflicting results obtained when a single specimen is examined by several techniques in the same laboratory Exactly the same problem is presented when two laboratories give discrepant results or when repeated specimens from the same patient tested in the same laboratory give first a positive then a negative again followed by a positive result.

In general and excluding disagreement between insensitive and sensitive Wassermann antigens conflicting serologic findings may be considered to have the same significance as a single report of doubtful Given conflicting reports whether between laboratories, different tests or different specimens there are usually only two possibilities to be considered by the physician —either (a) the positive report is a laboratory error or (b) the patient is actually syphilitic his serum containing such small quantities of reagin that it is detected only by a very sensitive technique. The decision as to which of these two possibilities is correct is sometimes extraordinarily difficult. In the rare individual a third possibility may have to be considered (c) that these conflicting results reflect a biologic false positive reactivity of the serum in the absence of syphilitic infection (page 524)

After a report of e g. *Wassermann negative precipitation test positive* has been received a more careful history frequently elicits a definite history of syphilitic infection with or without treatment. Failing this the tests should be repeated not once but again and again and in another laboratory if necessary until all possibility of doubt as to their significance has been eliminated. A few type cases will perhaps best illustrate the interpretation of these conflicting reports.

I

	Wassermann	*Flocculation test A*	*Flocculation test B*
Original report	Negative	Positive	Doubtful
Repeat	Negative	Doubtful	Doubtful
Repeat	Doubtful	Positive	Negative
Repeat	Doubtful	Positive	Positive
Repeat in another laboratory	Positive	Positive	Doubtful

Interpretation.—Serum contains small but definite quantities of reagin patient syphilitic

II

	Laboratory A	*Laboratory B*
Original report	Positive	Negative
Repeat	Negative	Negative
Repeat	Negative	Negative
Repeat	Negative	Negative
Repeat	Negative	Negative

Interpretation.—Original report of positive from Laboratory A, a laboratory error no serologic evidence of syphilis.

III

	Wassermann	*Flocculation test*
Original report	Negative	Positive
Repeat	Negative	Positive
Repeat in Lab A	Negative	Positive
Repeat in Lab B	Negative	Positive

Interpretation—The patient s serum is persistently Wassermann negative, and persistently precipitation test positive. If the precipitation reaction is reliable, and yields consistently negative results with normal subjects, such a series of persistently positive reactions must be considered to have the same significance as a series of positive Wassermann reactions. Any one of many factors may serve to inhibit complement fixation without affecting the flocculation phenomenon

The Examination of the Spinal Fluid

Only one change in the spinal fluid is pathognomonic of syphilitic involvement of the central nervous system This is the appearance of reagin (positive Wassermann or flocculation reaction) in the spinal fluid The other tests discussed in the following paragraphs (Table 119) are not specific for syphilis but serve only as indices of meningeal irritation whatever the cause of that inflammatory reaction

Cell count and differentiation —The cell count on spinal fluid to be of value, must be made within an hour after the fluid is withdrawn Less than 5 cells per cubic mm. of fluid is normal, a count of 5–10 cells is on the borderline of abnormality more than 10 cells is definitely abnormal. The predominant cell type in neurosyphilis is the lymphocyte A cell count on bloody fluid is valueless.

Qualitative and quantitative tests for an increase in spinal fluid protein —(Pandy Weichbrodt, Ross-Jones, etc.) The normal amount of protein in spinal fluid is from 10–35 mgms. per 100 cc Larger amounts than this are definitely abnormal. Although the tests for total spinal fluid protein are usually reported as 0 one plus two plus three plus four plus, it is apparent that this is an altogether arbitrary classification, and that to be of quantitative significance the protein content should be reported in actual mgm. per cent. If there were available simple procedures for the quantitative determination not only of total protein but of globulin as well, it would be unnecessary to perform the so-called colloidal tests, which merely reflect the protein pattern of the cerebrospinal fluid.

Colloidal reaction (colloidal gold mastic benzoin etc) —The preparation of colloidal gold solution is so elaborate and so subject to technical error that many laboratories have abandoned it in favor of the much simpler and equally satisfactory colloidal mastic It is now generally agreed that the precipitation of these colloidal suspensions by spinal fluid is due to the presence in spinal fluid of increased amounts of globulin and that the particular zones of precipitation ("paretic" "middle zone" "meningitic) depend on the balance of albumin and globulin (Eagle)

It seems clear also that the type of zone precipitation observed (the so-called colloidal curve) is actually of no significance in the differentiation of clinical types of neurosyphilis. Thus the paretic type of curve, while

TABLE 119

CEREBROSPINAL FLUID IN DIFFERENTIAL DIAGNOSIS OF NEUROSYPHILIS

			Cells per cu. mm.	Protein (Pandy's test)	Protein mgm. per 100 cc.	Wassermann titre†	Colloidal test (gold or mastic)
Normal fluid			0–5	0	15–30	Negative with 1 0 cc	0000000000 to 2222110000
Bloody tap normal fluid			Excess of W B C depends on amount of blood	± to +	Slight increase	Negative with 1 0 cc	Variable
Asymptomatic early or late	Minimal involvement	Group 1a	5–30	0	Normal	Negative with 1 0 cc	Negative
	Minimal involvement	Group 1b	5–30	± to ++	30–75	Negative with 1 0 cc	Negative
	Intermediate group	II	0–100	± to ++	Moderate increase	Positive with 0.2 cc or larger amounts	Variable
	Paretic formula	III	10–200	++++	50–200	Positive with 0.2 cc or smaller amounts	5554321000
Acute syphilitic meningitis			50–2000	++++	50–200	Negative, or variably positive	Variable, often 5555543210 or 1135555310
Late meningovascular			5–100	± to ++++	Moderate increase	Positive with 0.2 cc or larger amounts	Variable
Tabes dorsalis			0–100	0 to ++++	Normal to marked increase	Negative, or variably positive	Negative to 1123443210 or 5555432100
General p[illegible]			10–200	++++	75–200	Positive with 0.1 cc or smaller amounts	5555554321
[illegible]urosyphilis			0–50	0 to ++	Normal to moderate increase	Negative or positive with large amounts	Negative or variable

* Measurements of spinal fluid pressure, determination of subarachnoid block by jugular compression, and chemical determination of sugar, chloride, and non-protein nitrogen are rarely of value in the differentiation of types of neurosyphilis. C.C.G. classification.

† The amounts of spinal fluid indicated in this column are re[illegible]ed to a technique employing 0.2 cc. of all the other reagents

etically uniform in paresis occurs in other forms of neuraxis involvement as well and it is of value only in that if persistent under treatment suggests the possibility of the future development of paresis No importance of any kind attaches to slight precipitation, reading no higher than 2, in colloidal gold or mastic curves.

In the absence of a positive spinal fluid Wassermann an increase in cell count and protein and an alteration in colloidal curve indicate only meningeal irritation which may be due to many causes other than syphilis. Any process which causes meningeal irritation whether brain or cord tumor multiple sclerosis bacterial encephalitis meningitis or even simple spinal puncture may result in the appearance of increased cells and protein in the spinal fluid and of zones of precipitation in the colloidal reactions, as an exudative reaction. Nevertheless these abnormalities in a patient known to have syphilis are entirely adequate evidence in favor of a diagnosis of neurosyphilis unless there is some other obvious explanatory cause. Only too often have we seen such minor changes disregarded because the fluid Wassermann was negative the patient later returning with full-blown clinical evidence of neurologic damage. In early neurosyphilis protein may be increased and the colloidal curve altered before the Wassermann becomes positive in some instances of late neurosyphilis these tests may be abnormal though the Wassermann is negative and may remain so long after the specific Wassermann reagin has completely disappeared under the influence of treatment.

Wassermann and flocculation tests on the spinal fluid—A positive Wassermann or flocculation reaction in the spinal fluid* is absolute evidence of syphilitic involvement of the central nervous system by the *T pallidum* and probably is a measure of tissue involvement as well. The only exceptions to this statement are those rare instances in which a syphilitic patient with a positive blood Wassermann develops an acute pyogenic (pneumococcus meningococcus or tuberculous) or aseptic (lymphocytic) meningitis. In six such patients we have seen a previously negative fluid Wassermann become positive during the acute inflammatory process to revert to negative after its subsidence. This phenomenon undoubtedly depends on an alteration of the blood-spinal fluid barrier and a passage of reagin from blood to spinal fluid which in more normal circumstances is inhibited.

For various technical reasons (Eagle) precipitation tests on spinal fluid are usually less satisfactory than an adequate Wassermann test. *The proper interpretation of the spinal fluid Wassermann in syphilis demands that the test be quantitatively titered.* This quantitative titration of the fluid reagin content is of value not only in diagnosis, but also in following the progress of treatment. With a Wassermann technique employing 0.2 cc. of each reagent the test on spinal fluid should be done on

* An anticomplementary Wassermann reaction in a fluid freshly withdrawn and free from bacterial contamination is usually the equivalent of a strongly positive result as shown by quantitative titration. This does not apply to fluids several days old, which have become cloudy with bacteria on standing; such fluids tend to become both hemolytic and anticomplementary

amounts ranging from 0 1 to 1 0 cc. and if positive with the smaller quantity the titration should be carried downward In certain types of neurosyphilis especially paresis a positive Wassermann may be obtained with quantities of fluid as small as 0 001 cc.

As with other spinal fluid tests no direct conclusions as to the type of neurosyphilis can be drawn from the fluid Wassermann alone.

The 'pattern of spinal fluid abnormalities is however of considerable value in differential diagnosis between types of neurosyphilis. This is especially true of the so-called 'paretic formula, consisting of a cell increase of 10–200 or slightly more marked increase in protein and globulin (Pandy four plus protein 75–200 mgms. per 100 cc.) a Wassermann test strongly positive in amounts of fluid ranging between 0 001 and 0.2 cc. and a colloidal curve showing a wide zone of precipitation beginning with the very first tube of the test. This formula is almost constant in paresis. It may also occur in other types of neurosyphilis but prolonged observation of such patients has shown that the possibility of the subsequent development of paresis is great.

Under the influence of treatment the cell count is usually the first to return to normal the Wassermann next, but much more slowly and increased protein and abnormal colloidal curves last of all This however is not invariable. The utilization of spinal fluid examinations as a measure of the effectiveness of treatment is more fully discussed in Chapters XXI and XXIV

The Serologic Response to Treatment

In evaluating the serologic response to treatment the physician must bear in mind the qualitative nature of the serum tests A patient tested week by week during treatment may at first give a persistently positive serum reaction the appearance of a doubtful reaction 4 8 or 16 weeks after the beginning of treatment indicates that reagin has almost completely disappeared from the serum and presages the appearance of negative blood tests in the near future if treatment is continued. Actually such a series of tests (positive positive positive doubtful doubtful, negative negative) tells very little of the quantitative changes in the serum reagin content during treatment When first tested the serum may have been positive whether by a Wassermann or flocculation test in a dilution of 1 100 as a result of treatment, this reagin titre may have fallen week by week to 75 75 50 50 25 5 the routine qualitative test remaining positive all the while and it is only at the finish of the curve when reagin has almost completely disappeared that the physician obtains the first serologic evidence of improvement in the appearance of doubtful and subsequently negative reports. Nevertheless since there is as yet no satisfactory evidence that either the initial reagin titre or the rate at which that titre falls under treatment is of prognostic significance quantitative serum tests in the ordinary case furnish but little information of practical utility

Serologic cure —It must further be borne in mind that serologic reversal from positive to negative whether spontaneous or effected by

treatment, is not synonymous with biologic cure indeed a report of negative need not even imply serologic "cure." It may mean only that the amount of reagin in the serum is less than that detectable by the particular methods employed. Frequently such a serum will be positive if tested by a more sensitive technique, or by the same technique on another occasion.

In treated syphilis the value of serologic negativity for the determination of "cure depends not on a single test but on a series of tests repeated over a long period of time. The relative worth of serologic control as a criterion of a satisfactory outcome in various types of syphilitic infection early or late has been discussed under the appropriate chapter headings

The so-called provocative Wassermann —It has been generally believed for many years that following the first injection of an arsenical drug into a syphilitic patient there is a provocative rise in the serum reactivity Previously negative or doubtful tests are said to become definitely seropositive while in patients already positive the serum reagin titre may be increased. The phenomenon has been widely used as an aid to diagnosis in patients giving inconclusive serum tests and clinical findings suggestive but not diagnostic of syphilitic infection However recent work by Eagle, Mohr Hogan and Kemp casts serious doubt on the actual existence of the provocative phenomenon. It would appear from their studies in both syphilitic men and rabbits that the apparent rise in reagin titre often observed soon after the administration of an arsenical is an artefact which rests on chance variations in the sensitivity of the laboratory tests and does not reflect an actual change in the serum reagin content. When an entire series of specimens taken from a patient before and after the institution of treatment were tested simultaneously the reagin titre was found to be essentially constant. Only in cases with very early syphilis did they observe an actual increase in the reagin titre following treatment (cf the curve for seronegative primary syphilis in Fig 88) and since that increase was observed only in patients and animals in whom the reagin titre was already on the rise it could not properly be ascribed to the treatment. Although the provocative phenomenon is apparently of no value in the diagnosis of syphilis these observations bear out the advisability of repeated blood tests without treatment, with multiple techniques and in different laboratories in cases where there is good reason to suspect syphilitic infection.

Seroresistance

(Reagin Fastness Wassermann Fastness)

Seroresistance in the adequately treated patient is a most disconcerting situation for both patient and physician This phenomenon has been discussed under various chapter headings, but it is desirable to summarise the available information in a single section

There is no general agreement as to what constitutes seroresistance One physician means by the term a permanently irreversible test the patient remaining seropositive no matter how much treatment he may receive

another uses the phrase in relation to a definite time period or a definite amount of treatment. For the purposes of this discussion seroresistance is arbitrarily defined in early syphilis as failure to reverse the serologic tests to negative within 6 months of treatment, and in late syphilis as failure to reverse within 12 months of treatment.

It must be emphasized first of all that the frequency of seroresistance in any stage of syphilitic infection is directly dependent on the sensitivity of the test employed. Within the last 15 years the laboratory has pro-

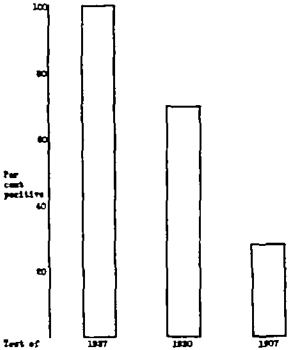


FIG. 89.—The influence of the type of serologic test employed on the incidence of seroresistance (Moore and Padget).

gressed from the relatively insensitive Wassermann technique with water bath incubation to the much more sensitive icebox test to more strongly fortified antigens to the sensitive flocculation techniques and, finally to the hypersensitive (often non-specific) screen procedures. Each successive step has resulted in a significant increase in sensitivity over the previous phase. Thus as shown in Fig 89 of 100 patients seroresistant as judged by the serologic tests in use in 1937 70 per cent would have been seroresistant according to the serologic standards of 1920 and only 28 per cent according to the tests in use in 1907. The incidence of seroresistance has therefore increased more than threefold between the years 1907 and 1937 as a result of improved serologic procedures alone. Each technical improvement has brought disappointment to physicians and patients in revealing that what seemed to be permanent serologic reversal

with the less sensitive technique, was actually not so that on the contrary and in spite of prolonged treatment, the test with a more sensitive technique remained persistently positive albeit at a low level of reagin content. Thus measured by improved serologic standards, results of treatment in all types of syphilis are seemingly becoming less satisfactory and will continue further in this direction with further advances in laboratory technique

In late syphilis one frequently observes patients whose qualitative blood tests vacillate back and forth between positive doubtful and negative week after week, without ever becoming permanently negative despite continued treatment. Such patients also belong to the seroresistant group their serum reagin content remaining more or less constant at a low level just on the borderline of the amount detectable by the test in question. On occasions when the test is slightly more sensitive (and laboratory variations in sensitivity are unavoidable particularly with the Was-

> The serologist is more often responsible for seroresistance than is disease (increasingly sensitive tests)
> Worry more about the laboratory- less about the patient.

FIG. 90.

sermann reaction) these sera are positive If the test is a little less sensitive, they are apparently negative and on yet other occasions the result is doubtful (Mohr and Smith) At any rate in a treated patient a series of tests such as positive, doubtful positive negative positive, negative doubtful, indicates the persistence of small quantities of reagin.

This fact may be clearly demonstrated by the use of a quantitative as opposed to a qualitative serologic test. In most laboratories the serologic test, whether a complement-fixation or a flocculation technique is qualitative that is, a standard amount of whole serum is employed and the results expressed in terms of positive, doubtful, or negative, are referred to this amount of undiluted serum. With the Kolmer modification of the Wassermann test, there is partial quantitation, the amounts of whole serum commonly employed being 0025 005 025 05 and 1 cc. But (and this is a very important "but") both in early and late syphilis any serologic test may be positive with minute amounts of serum i.e. as little as 0 000125 cc. The routine report, however does not disclose this fact It is only positive, four plus or whatever other term is used to convey the fact of positivity equally with the report of the patient whose serum contains only 1/100 as much reagin Under treatment there may be a rapid fall in the reagin content of the more strongly positive serum toward the level of negativity while the less strongly positive test, under an equal amount of treatment remain quite unchanged In both cases the patient is classified as seroresistant or reagin-fast though in fact one has been

improving steadily from the serologic standpoint, while the other has shown no improvement These statements may be expressed diagrammatically as in Fig 91.

The quantitative serologic technique holds great promise for an investigation of the puzzling features of seroresistance and the problem is now being investigated along these lines in our own clinic and laboratory However it is essentially a long term study involving many patients

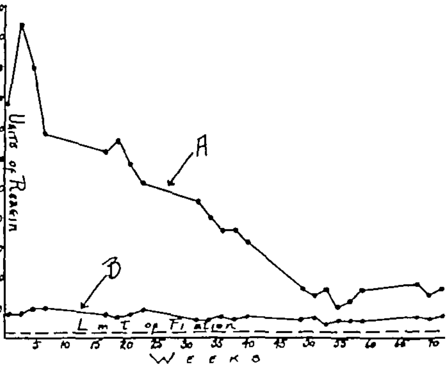


FIG. 91 —Two types of seroresistance in late syphilis are illustrated. In both cases, repeated specimens taken throughout the course of treatment were quantitatively titered, and the results expressed as the units of reagin present in the blood. The line of dashes at the bottom of the figure, marked "limit of fixation, indicates the approximate amount of reagin necessary to give a definitely positive result with the "routine" Wassermann test (approximately 2.5 units on the arbitrary scale used in the figure) The amount and duration of treatment are expressed in weeks.

Both patients are seroresistant at all times by the routine test. In patient A, however there has been marked reduction in serologic titre In patient B, treatment has been without serologic effect The significance of these two types of response cannot yet be interpreted.

and much time so that at present it is not possible to apply it to a discussion of the immediate practical aspects of seroresistance which must be conducted on the basis of the information available from the older qualitative technique

The cause of seroresistance is not known The two most tenable theories

The assumption that antisyphilitic treatment, particularly arsphenamine might in itself produce a false positive serologic test or contribute to the cause of sero-

are (1) that reagin continues to circulate in the blood even after treponemes have been destroyed by treatment and that persistently positive tests are indicative of a resistance to syphilis in somewhat the same manner as a positive Widal reaction is indicative of immunity to typhoid (2) that the reagin in the blood is elaborated by foci of infection which persist in spite of treatment. Neither of these theories is proved. Nevertheless in the management of the patient, one must differentiate between seroresistance in early and late syphilis. In the former seroresistance

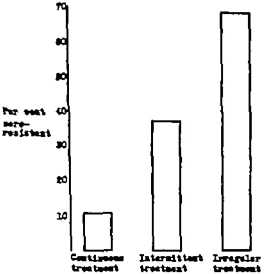


FIG. 92.—Relationship between the system of treatment employed and the incidence of seroresistance in patients with early syphilis (from data of C.C.G.)

must be considered in the light of our present knowledge, to indicate the presence of foci of treponemes from which progression or even redissemination of the disease might occur. Under these conditions serologic reversal is highly desirable. In contrast in late syphilis, serologic response to treatment is relatively unimportant since as will be shown later the ultimate clinical outcome cannot be measured by the results of blood tests.

Seroresistance in early syphilis.—The study of the C C G shows quite clearly that in early syphilis, seroresistance (i.e. persistently positive serologic tests for at least 6 months of treatment) is largely traceable to the system of treatment employed. As shown in Fig 92 it occurs in only 10 per cent of patients whose treatment for early syphilis is continuous in contrast to an incidence of 35 per cent among patients whose treatment is intermittent and 70 per cent in those whose treatment is irregular.

resistance (Strickler) has apparently been refuted by the subsequent work of Boas and Kissmeyer Kolmer and Kildaffe. There is no satisfactory evidence that treatment *per se* is a cause of seroresistance.

Aside from the type of treatment employed, or of lapses (rest periods) in any form of treatment the most important discoverable factor in early syphilis responsible for the phenomenon is involvement of the central nervous system Here the incidence of seroresistance stands in direct relation to the incidence and extent of spinal fluid abnormalities (asymptomatic neurosyphilis) The data covering this point again taken from the C C G study are shown in Fig 55 (see p 351) Thus in a patient with early syphilis failure to obtain serologic reversal by the end of 6 months of continuous treatment strongly suggests the possibility of asymptomatic neurosyphilis and calls for immediate study of the cerebrospinal fluid, if this has not already been done.

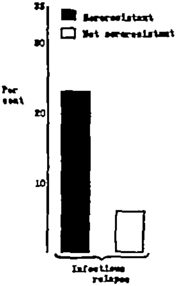


FIG. 93.—Relationship between seroresistance and infectious relapse in early syphilis (Moore and Padget)

In addition to this association there is in early syphilis a definite relationship between the occurrence of infectious relapse and seroresistance. This is shown by Fig 93 All the patients included in this compilation were adequately treated. However infectious relapse occurred more than four times as frequently (23 per cent) among patients who were seroresistant than among patients who experienced prompt serologic reversal (5 per cent) This observation is not to be confused with the earlier observation of Moore and Kemp that infectious relapse occurs more frequently among patients with seronegative secondary syphilis and those whose serologic test reversed 'prematurely' than among those whose tests reversed at about the expected time (cf page 223)

The management of patients with early syphilis who are seroresistant according to this definition (for 6 months of treatment) is outlined according to Moore and Padget, as follows

I Examine the cerebrospinal fluid
   A. If reaction is positive Alter system of treatment to that for early asymptomatic neurosyphilis
   B If reaction is negative
      1 Eliminate rest periods—treatment must be continuous.
      2 Employ full dosage of a potent arsphenamine
      3 Prolong treatment for a full year of weekly injections after serologic reversal is obtained

In the majority of those whose spinal fluids are negative further *continuous* treatment will reverse the serologic tests to negative *After reversal of the serologic test treatment should be continued for one full year* If the test remains positive a minimum of three years continuous treatment is necessary

Under these circumstances of management, there is no evidence that seroresistance in early syphilis (perhaps a better term would be "delayed reversal," since in the majority of instances reversal may be ultimately secured) carries any serious prognostic import from the clinical standpoint for the patient's future course. Such patients seem to remain clinically well in as high a proportion of cases as those in whom a more prompt reversal is brought about.

Seroresistance in late syphilis —Seroresistance in late syphilis occurs so frequently that it is often the bane of the syphilologist as well as of the practitioner In the past, almost every year witnessed the publication of many papers suggesting the use of this or that drug or of this or

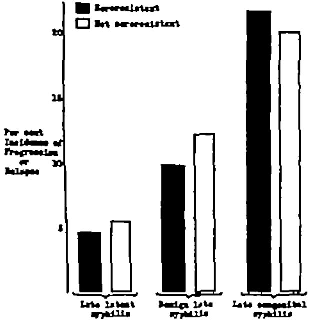


FIG. 94.—Lack of relationship between seroresistance and the incidence of progression or relapse in patients with various forms of late syphilis. (From data of the C.C.G., Dissker Wasserman and Goodman, and Smith.)

that method of non-specific therapy for the treatment of patients with fixed serologic tests Fortunately enough information has now accumulated to permit an accurate evaluation of this problem

In contrast to early syphilis seroresistance in late syphilis does not carry with it the implication of clinical progression or relapse This is illustrated by Fig. 94. For the three types of late syphilis considered in this figure, the incidence of progression or relapse was practically the same among patients who were seroresistant and those who were not. In fact, patients with seroresistant latent and benign late syphilis seemed to fare somewhat better than those who experienced serologic reversal Thus progression or relapse developed in 4 6 per cent of the patients with

late syphilis who were seroresistant in contrast to 5.7 per cent of those who were not in benign late syphilis these eventualities developed in 9.8 per cent of the seroresistant group in contrast to 12.2 per cent in whom serologic reversal was accomplished. In late congenital syphilis progression or relapse was encountered in 21.5 per cent of patients who were seroresistant and 20.0 per cent among those who were not. These findings suggest that in some types of late syphilis seroresistance may be beneficial rather than harmful.

The incidence of seroresistance in patients with various types of syphilitic infection who have been given adequate modern treatment is as shown in Table 120.

TABLE 120

THE INCIDENCE OF SERORESISTANCE IN VARIOUS TYPES OF SYPHILITIC INFECTION
(Early syphilis treated for at least 6 months, late syphilis for at least 1 year)

Type of syphilis		Percentage of seroresistance with adequate treatment
Early Syphilis (primary and secondary)		5–15
Latent Syphilis		35
Late Cutaneous and Mucosal		50
Late Osseous		65
Late Visceral (hepatic, etc.)		50–70
Late Cardiovascular		50
Central nervous system	Meningeal	10–20
	Meningovascular	40–50
	Tabes	10–25
	Paresis	70–80
Early Congenital		5–20
Late Congenital		60–80

These data indicate that seroresistance may be an accompaniment of grave rather than of trivial syphilis. They also indicate the proper procedure for the physician confronted with a seroresistant patient. The important thing is not to attempt various modifications of treatment procedure in order to reduce the serologic test to negative but to investigate the patient thoroughly to determine if possible factors which may be responsible for keeping the test positive (see Fig. 95). If the original examination has not disclosed the presence of a lesion in one of the organs or systems enumerated complete physical re-examination should be performed with careful emphasis particularly on cardiovascular osseous and central nervous systems. The accessible bones should be carefully palpated (not forgetting to inspect the nasal septum curiously enough, the relatively trivial lesion of gumma of the nasal bone is often apparently responsible for seroresistance) and any roughening or thickening checked by x-ray examination. The spinal fluid must be examined neurosyphilis may be asymptomatic rather than clinically apparent. Not until after the performance of such a searching physical and laboratory examination is it profitable to discuss the treatment of seroresistance.

If the apparent cause of the persistently positive blood test is either cardiovascular visceral or central nervous system syphilis the proper

treatment to be instituted is the treatment of these conditions (see the appropriate chapters) and no attention whatever need be paid to the question of ultimate reversal of the serologic test. The desideratum of treatment is not to render the blood test negative but to relieve symptoms prevent clinical progression and prolong life. If these three aims can be accomplished, it makes no difference to the patient or physician whether the serologic test is positive or negative

I. Examine the cerebrospinal fluid

II. Conduct a searching clinical study for lesions of syphilis, with particular reference to
   A. The cardiovascular system (including roentgenologic examination)
   B. The central nervous system
   C. The bones

III If abnormalities in any of these systems are discovered, plan treatment accordingly

IV If no abnormalities are discovered
   A. Prolong treatment to a minimum of two years, continuously and with full doses
   B. Follow the patient for the rest of his life, with, periodically complete and searching resurveys of his clinical status
   C Frankly discuss and fully explain the situation to the patient and give him as much reassurance as possible

FIG. 95.—The Management of Patients with Seroresistant Late Syphilis (Moore and Padget)

If the apparent cause of seroresistance is cutaneous, osseous or late congenital syphilis, and if no evidences of cardiovascular visceral or central nervous system involvement are present, the patient may be regarded as in the same category as seroresistant patients with latent syphilis. Obvious lesions if present almost always heal promptly and relapse is no more frequent than in patients who are not seroresistant. Treatment may proceed, therefore not on the basis of lesions actually detectable (as in cardiovascular visceral or neurosyphilis) but on the basis of a suspicion that as evidenced by seroresistance such potentially grave lesions may be present but below the level of clinical recognition The treatment of the seroresistant patient with late congenital, osseous or latent syphilis is thus prolonged not because of lesions which the patient actually has, but because of lesions which if untreated he may develop It is customary in many clinics our own included to treat such patients continuously with an arsenical preparation and a heavy metal in alternation for a minimum period of two years. No special attempts are made by utilizing other than the usual drugs by intensification of treatment or by the

R. B.: On the Presence in Syphilitic Serum of Antibodies to Spirochetes their Relation to so called Wassermann Reagin, and their Significance for the Serodiagnosis of Syphilis, J Exper Med 71 215 1940—Eagle H. Mohr C. F., Hogan R. B., and Kemp, J E. On the Supposed Provocative Rise in the Reagin Titer of Syphilitic Serum Following the Administration of Arsphenamine, to be published—Erickson, P T., and Eagle, H. Evaluation of Spirochete Complement Fixation Reaction in Comparison with the Eagle Flocculation and Wassermann Procedures Ven. Dis. Inform. 21 31 1940—Gaehtgens W: Über die antigene Wirkung von Pallidasuspensionen in carbolisierter Kochsalzlösung, Med Klin. 25 390 1929—Hazen, H. H. Senear F E., Parran, T., Sanford, A. H., Simpson W M, and Vonderlehr R. A. Serologic Evidence of Syphilis in Malarial Patients, Arch Dermat. & Syph. 37 431 1938.—Kahn, R. L.: A Serologic Verification Test in the Diagnosis of Latent Syphilis, Arch. Dermat. & Syph 41 817 1940—Kahn, R. L. McDermott, E. B., and Marcus, S. (a) Effect of Temperature on Kahn reaction. I With Serologically Positive Sera of Lower Animals, Am. J Syph Gonor & Ven. Dis. 25 151 1941 (b) Effect of Temperature on Kahn reaction. II With Serologically Positive Sera of Human Syphilis, ibid. 25 157 1941 (c) Effect of Temperature on Kahn reaction III With Serologically Positive Sera in the Absence of Syphilis, ibid. 25 162, 1941 (d) Effect of Temperature on Kahn reaction IV With Serologically Negative Sera in the Absence of Syphilis ibid 25 173 1941—Kitchen S. F., Webb, E L., and Kupper W H.: The Influence of Malarial Infections on the Wassermann and Kahn Reactions J.A M.A 112 1443 1939—Kolmer J A. Serologic Reactions and Immunity in Relation to Infection and Treatment of Syphilis, Am. J Syph. Gonor & Ven. Dis. 22 426 1938—Mohr C. F., Moore J E., and Eagle H. Biologic False Positive Serologic Reactions for Syphilis. (a) I Occurring in Normal Individuals (b) II. Associated with Organic Diseases other than Syphilis Arch Int Med. in press.—Mohr C. F., and Smith, C. A. On the Supposed Daily Variation of the Reagin Content of Syphilitic Serum, Am. J Syph. Gonor & Ven. Dis. 24 322 1940—Moore J E., Cole H. N O'Leary P A., Stokes, J H. Wile U J., Clark, T., Parran T Jr., and Usilton, L. J Cooperative Clinical Studies in Treatment of Syphilis Latent Syphilis III Clinical Progression and Relapse Wassermann Fastness and Death Ven. Dis. Inform 13 389 1932.—Moore J E., and Eagle H.: The Quantitative Serologic Test for Syphilis. Its Variability Usefulness in Routine Diagnosis and Possible Significance A Study of 1665 Cases, Ann. Int. Med 14 1802 1941—Moore J E., Eagle H., and Mohr C. F Suggested Method of Approach to the Clinical Study of Biologic False Positive Tests for Syphilis, J.A M A. 115 1002, 1940—Moore, J E., and Kemp, J E.: Treatment of Early Syphilis. III Wassermann Reaction in Treated Early Syphilis Bull Johns Hopkins Hosp. 39 36, 1926.—Moore J E., and Padget, P The Problem of Seroresistant Syphilis, J.A M.A. 110 96 1938—Parran T., and Emerson K. The Effect of Tuberculosis on the Serological Reactions for Syphilis, Am Rev Tuberc 30 1 1939—Sherwood, N P., Bond G C., and Canuteson, R. I.: On the Possible Presence of a Reagin-like Factor in Normal Human Serum, Am J Syph. Gonor & Ven. Dis 25 179 1941—Sherwood, N P., Bond, G C., and Clark, H. F Results Obtained with the Kolmer Kahn, and Kline Tests on Animal Sera Am. J Syph. Gonor & Ven. Dis. 25 93 1941—Strickler A., Munson, H. G., and Sidlick, D M Positive Wassermann Test in Non-syphilitic Patients after Intravenous Therapy J A M.A 75 1488 1920—Wasserman, H., and Goodman M J Results of Treatment in Late Mucocutaneous and Osseous (Benign Late) Syphilis Am J Syph & Neurol 18 458 1934

Chapter XXIX

THE THERAPEUTIC TEST, THE NON-SPECIFIC EFFECTS OF ANTISYPHILITIC TREATMENT, THE LUETIN TEST

The Therapeutic Test

The differential diagnosis between syphilis and some other condition can sometimes be settled only by means of treating the patient for syphilis and observing the effect. This situation usually arises when the patient is known to have syphilis on the grounds of definite history physical findings or serologic tests and in addition symptoms or a lesion which may be due to some other cause. Less frequently since the increase in delicacy of modern serologic methods, does confusion occur as to whether or not syphilitic infection is actually present. Though the therapeutic test is therefore of less practical importance than formerly it is essential to mention briefly the conditions under which it is usually applicable and to outline methods of procedure.

The therapeutic test in suspected early syphilis.—When the patient's lesions are such as to arouse suspicion of the diagnosis of primary or secondary syphilis the therapeutic test is not justifiable. Proof of infection is obligatory before treatment is started including the demonstration of treponemes by darkfield or positive serologic tests or both. If these cannot be demonstrated at the first visit delay further observation and repeated laboratory examinations must be insisted upon.

The therapeutic test in suspected late syphilis.—In the case of skin or mucosal lesions diagnostic confusion most frequently arises as between syphilis and tuberculosis (lupus vulgaris) fungus infections (actinomycosis blastomycosis sporotrichosis) chronic leg ulcers (usually varicose) or neoplasms. Two average therapeutic doses of any arsenical drug (0.3–0.4 gm. arsphenamine, 0 06 gm. mapharsen 0 6–0 75 gm. neoarsphenamine) given at 4–7 day intervals will settle the issue If the lesion is due to syphilis healing should be far advanced or complete within 10–14 days. While the arsphenamines cause some non-specific healing in fungus infections or cutaneous tuberculosis, it is not so rapid as in syphilis. Other methods of diagnosis bacteriologic for identification of the causative organism radiologic for the possible demonstration of syphilitic bone lesions underlying or close to a suspicious skin lesion or histologic should not be neglected.

Neoplasm is less frequently a cause of confusion on cutaneous than on mucosal surfaces. The clinical differentiation between carcinoma of the tongue or sarcoma of a tonsil and gumma may be impossible. In this situation however as when there is confusion between syphilis and neoplasm anywhere in the body the neoplasm takes first place if it is apparently operable Biopsy with preparations for immediate operation electrodesiccation or coagulation, or radiation takes precedence over therapeutic

tion the lesion should be inspected at frequent intervals if possible 24–48 hours after the first injection for evidences of therapeutic shock, and at 3–7 day intervals for evidences of healing

The choice of drugs for the therapeutic test varies a little according to the diagnostic problem. When the lesion may be due to tuberculosis or one of the fungus infections iodides are contra-indicated since they exert the same effect in these conditions as in syphilis. An arsenical preparation is utilizable in all situations excepting suspected cardiovascular or hepatic syphilis provided its non-specific effect on the lesions of other diseases than syphilis is taken into consideration in evaluating results Should the therapeutic test prove positive treatment for syphilis must be continued and prolonged in accordance with the type of lesion which the patient presents If a therapeutic test in a patient with known syphilis discloses the presenting lesion to be due to some other cause the question of continuing further with antisyphilitic treatment and its character will often depend largely on the nature of the complicating disease Should this prove to be some such uniformly fatal condition as inoperable neoplasm Hodgkins' disease etc. there is little point in adding to the patient's discomfort with additional treatment for syphilis

The Non-Specific Effects of the Arsphenamines

Reasoner and Nichols have published a valuable article describing the use of the arsphenamines in other diseases than syphilis. In yaws they are as rapidly effective as in syphilis and the methods of treatment employed are practically identical Rat-bite fever is promptly and completely curable with one or two injections of the arsphenamines and if given during the febrile stage they are curative also in the majority of cases of relapsing fever (Dicuaide*) Spirochetal jaundice (Weil's disease) is apparently uninfluenced by them. Certain patients with broncho-pulmonary spirochetosis have certainly been rescued from death by the intravenous use of these drugs

Local fuso-spirillary infections (Vincent's angina, gangrenous balanitis broncho-pulmonary spirochetosis) are benefited more by local than by systemic treatment with the arsphenamines, which may be applied to easily accessible lesions in the mouth or on the genitalia as a powder suspended in a small quantity of glycerin or in aqueous solution. Even better as a local application is a 5 per cent aqueous solution of chromic acid. The intravenous injection of arsphenamine is not advised by us and if used it should be employed only after the patient's blood has been tested for syphilis. We have seen many instances where dentists have given neoarsphenamine for what was thought to be Vincent's angina to patients who had undoubted secondary syphilis Still worse we have seen two serious cases of arsenical hepatitis and know of a death from hemorrhagic encephalitis in patients with Vincent's stomatitis inadvisedly treated with an arsphenamine intravenously It is an indefensible procedure to use a potentially [illegible] drug in the treatment [illegible] hat is usually a mild and localize[illegible]

Personal commu[illegible]

Chapter XXIX

THE THERAPEUTIC TEST, THE NON-SPECIFIC EFFECTS OF ANTISYPHILITIC TREATMENT; THE LUETIN TEST

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testing During the time wasted on the latter metastasis may occur, and a hopeful situation transformed into a hopeless one. If on the other hand, the lesion is apparently inoperable the therapeutic test may be used. Again two injections of an arsenical will tell the story

The clinical differentiation of tuberculous *versus* gummatous adenitis is rarely possible. One may exactly simulate the other Under antisyphilitic treatment gummatous adenitis heals slowly requiring about 6 weeks of weekly injections of an arsenical tuberculous adenitis is little if at all improved

Syphilitic bone lesions may simulate pyogenic osteomyelitis tuberculosis, traumatic periostitis, Paget s disease or bone tumors. When such confusing lesions occur in an individual known to have syphilis a therapeutic test should be performed before resorting to what may prove to be a useless operation A single injection of an arsenical, if the lesion is syphilis usually causes first a prompt exacerbation of pain for the first 12–36 hours (therapeutic shock) followed by a rapid subsidence of discomfort and complete symptomatic relief

Almost all the various lesions produced by syphilis in the eye may be due to other causes. Inflammatory lesions of the uveal tract may for example be due to gonorrhea, tuberculosis rheumatic fever brucellosis or focal infection. If caused by syphilis however the response of all ocular inflammatory lesions except interstitial keratitis to 2–3 weeks of arsenical therapy is immediate If improvement does not occur other possible etiologic factors should be searched for The slow but definite non-specific response to arsphenamine of certain forms of non-syphilitic uveitis may result in the healing of lesions stubbornly resistant to other therapeutic procedures.

Stokes lays some stress on the value of the therapeutic test in cardiovascular syphilis particularly in aneurysm or in uncomplicated aortitis. He has seen several instances in which pulsation in a mediastinal mass previously absent appeared after several weeks of treatment with a heavy metal and potassium iodide or of suspected aortitis in which frank signs of cardiovascular syphilis replaced suspicious signs after treatment. In our experience the clinical differentiation of saccular aneurysm and solid mediastinal tumor has infrequently been difficult, and has not been aided by the results of therapeutic testing The distinction between syphilitic and rheumatic aortic regurgitation is sometimes impossible during life before or after treatment and the diagnosis of uncomplicated aortitis is better confirmed by years of observation than by a few weeks or months of therapeutic testing. In our own clinic serologic tests are positive in 95–98 per cent of all patients with previously untreated cardiovascular syphilis If a patient with an aortic lesion is known to have syphilis he had better be treated as if the diagnosis of syphilitic aortitis were certain. This involves several years of treatment (see Chapter XVIII)

In suspected hepatic syphilis the therapeutic test always with a heavy metal and potassium iodide never with an arsenical takes precedence over immediate exploratory operation At least 2 months of treatment with weekly intramuscular bismuth or daily inunctions of mercury to-

gether with 6–12 gms. of potassium iodide daily is necessary before deciding that no benefit has been obtained, though if the lesion is due to syphilis and is predominantly inflammatory clinical improvement and the melting of a palpable mass is often dramatically prompt.

In suspected gastric syphilis on the other hand we feel that exploratory operation should precede the therapeutic test. Malignancy is the common cause of confusion the only hope of cure, if the lesion is neoplastic is operation before metastasis. If the condition appears operable therefore, we advise exploration first and antisyphilitic treatment later If it is apparently inoperable of course the therapeutic test comes first One must not forget the possibility of a false positive therapeutic test in such conditions as gastric or duodenal ulcer or gastric carcinoma. Immediate symptomatic improvement may be striking only to be followed by subsequent relapse.

The therapeutic test is of little value in the differential diagnosis of neurosyphilis and other neurologic diseases.

Syphilitic fever —In late syphilis with or without involvement of the liver, there may sometimes appear prolonged fever continuous remittent or intermittent, and occasionally reaching remarkable heights (Futcher) In such instances there may be diagnostic confusion between syphilis, rheumatic fever malaria typhoid fever tuberculosis and septicemia. If syphilis is suspected the issue may be promptly settled by the therapeutic test. A single injection of an arsphenamine will usually result in disappearance of syphilitic fever within 24–48 hours or if arsphenamine seems inadvisable the temperature will fall to normal after 4–5 days administration of a heavy metal and the iodides.

Malignancy versus syphilis —Though we have repeatedly stressed the point elsewhere it deserves repeating separately, that when there is diagnostic confusion between syphilis and neoplasm anywhere in the body suspicion of neoplasm has the right of way provided the lesion is apparently operable. Therapeutic testing should be delayed until a biopsy has shown the non-malignant character of the lesion.

The physician must not forget that in certain instances of early syphilis in Negroes the generalized adenopathy may be so extreme as to simulate one of the lymphoblastomas (lymphatic leukemia, Hodgkins disease) and that in late syphilis in both races the mediastinal tumor of lymphosarcoma or Hodgkins' disease may easily be confused with syphilitic mediastinitis. Under these two sets of circumstances *if there is any doubt* as to whether syphilis is causing the lesion and if the doubt cannot be resolved by biopsy antisyphilitic treatment and radiation therapy should be given simultaneously the delay of waiting for the results of a therapeutic test may be serious.

General principles of the therapeutic test —Since a therapeutic test implies a measurable effect of treatment, it should be employed only in conditions in which the symptoms or the lesion are sufficiently definite to permit such an appraisal. Merely to have the patient feel better is not enough the tonic effect of arsphenamine will often produce this symptomatic result in non-syphilitic patients. Further the test implies observa

tion the lesion should be inspected at frequent intervals if possible 24–48 hours after the first injection for evidences of therapeutic shock and at 3–7 day intervals for evidences of healing

The choice of drugs for the therapeutic test varies a little according to the diagnostic problem. When the lesion may be due to tuberculosis or one of the fungus infections iodides are contra-indicated since they exert the same effect in these conditions as in syphilis An arsenical preparation is utilizable in all situations excepting suspected cardiovascular or hepatic syphilis provided its non-specific effect on the lesions of other diseases than syphilis is taken into consideration in evaluating results Should the therapeutic test prove positive treatment for syphilis must be continued and prolonged, in accordance with the type of lesion which the patient presents If a therapeutic test in a patient with known syphilis discloses the presenting lesion to be due to some other cause, the question of continuing further with antisyphilitic treatment and its character will often depend largely on the nature of the complicating disease Should this prove to be some such uniformly fatal condition as inoperable neoplasm, Hodgkins disease etc. there is little point in adding to the patient's discomfort with additional treatment for syphilis.

The Non-Specific Effects of the Arsphenamines

Reasoner and Nichols have published a valuable article describing the use of the arsphenamines in other diseases than syphilis In yaws they are as rapidly effective as in syphilis and the methods of treatment employed are practically identical Rat-bite fever is promptly and completely curable with one or two injections of the arsphenamines and if given during the febrile stage they are curative also in the majority of cases of relapsing fever (Dieulaide*) Spirochetal jaundice (Weil s disease) is apparently uninfluenced by them. Certain patients with broncho-pulmonary spirochetosis have certainly been rescued from death by the intravenous use of these drugs

Local fuso-spirillary infections (Vincent s angina, gangrenous balanitis broncho-pulmonary spirochetosis) are benefited more by local than by systemic treatment with the arsphenamines which may be applied to easily accessible lesions in the mouth or on the genitalia as a powder suspended in a small quantity of glycerin or in aqueous solution. Even better as a local application is a 5 per cent aqueous solution of chromic acid The intravenous injection of arsphenamine is not advised by us and if used it should be employed only after the patient s blood has been tested for syphilis We have seen many instances where dentists have given neoarsphenamine for what was thought to be Vincent s angina to patients who had undoubted secondary syphilis. Still worse we have seen two serious cases of arsenical hepatitis and know of a death from hemorrhagic encephalitis in patients with Vincent s stomatitis inadvisedly treated with an arsphenamine intravenously It is an indefensible procedure to use a potentially very toxic drug in the treatment of what is usually a mild and localized disease

* Personal communication

In addition to the spirochetal diseases, there is a long list of conditions in which in some instances the arsphenamines are unquestionably of non-specific benefit. These diseases include such relatively harmless skin conditions as psoriasis and lichen planus more serious cutaneous lesions such as sarcoid tuberculides of skin (also of bone) the fungus infections (blastomycosis, actinomycosis, sporotrichosis) pyelitis malaria non-syphilitic uveitis disseminated sclerosis and undulant fever In planning the treatment of any of these diseases, the risks of arsphenamine treatment should be carefully weighed against possible therapeutic benefit. There is as yet little information as to the non-specific effects of mapharsen.

Recently Osgood has published experimental and clinical studies which suggest that neoarsphenamine may be of value in subacute bacterial (*S viridans*) endocarditis.

The Luetin Test

As a practical procedure, the luetin test and its various more recent modifications are of little or no value either in diagnosis (Bessemans Dujardin and Wiser) or as evidence of the curative effects of treatment. These tests are important from the standpoint of clinical investigations bearing on the study of allergy and immunity but as yet they have no definite practical application.

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CHAPTER XXX

SYPHILIS AND MARRIAGE

In most patients with syphilis the relationship of the infection to the marital state is a problem which sooner or later the physician must aid in solving. An individual already married is found to be infected: what shall be done about the marital partner? An unmarried patient desires to marry: shall he be given permission to do so? These are questions impossible to evade and on their satisfactory answer may depend the welfare and happiness of several persons. In the following paragraphs we shall provide our point of view, purposely avoiding consideration of the many published discussions of others.

Syphilis Discovered in a Married Person

Disclosure of the diagnosis to the marital partner.—Whether the patient's infection is recent or remote, the marital partner should be told of the diagnosis. The average patient recoils at this idea: he sees his home disrupted and divorce staring him in the face. This danger is more imaginary than real: the facts may be presented in such a way as to protect the patient, to avoid the moral issue, and to cement rather than loosen the marital bond. When the ordeal is over the patient is relieved of the dual anxiety of feeling that he is concealing a guilty secret and of worry as to whether his family is also infected. The average wife receives the news not with the contumely and reproach that the husband expects but with added sympathy for his difficulties.

Frankness is desirable from the three standpoints of protection of spouse, patient and physician. The patient's sense of fair play may be enlisted as to the spouse. She must be examined to determine the presence or absence of infection; if infected, she must be given the benefit of treatment; if uninfected, she must be protected against the disease. This argument involves such an elementary spirit of justice that only the rarely selfish patient is able to withstand it. While it is true that the essential examinations may be made, if it is absolutely necessary, by means of various subterfuges rather than for the avowed purpose of detecting a possible syphilitic infection, such subterfuges involve the risk of accidental rather than purposeful disclosure.

It is from this very contingency that the patient must be protected. If he refuses a frank discussion, he risks accidental disclosure not only through the examination of the spouse but in various other ways. He may ultimately find it impossible satisfactorily to explain why he must visit a physician weekly; why he has no appetite for dinner every Wednesday evening; why attacks of nausea occur at exact weekly intervals; why clothing is stained at the elbow with a spot of blood; why he must go to bed for two days for a spinal puncture. The unsuspecting wife or husband

repeating these strange coincidences to a better informed but indiscreet friend has implanted a seed of suspicion which if it grows into certainty is provocative of far more resentment at the attempted concealment than would have arisen from honest discussion at the beginning A disrupted home and divorce are much more likely if the spouse learns of the trouble from outside sources than from the patient.

Finally, frankness is desirable from the standpoint of the physician. It is difficult to imagine a more embarrassing event than the arrival in the physician's office of a patient s wife who by virtue of her ignorance that her husband has syphilis, has contracted the disease herself or who, perhaps has borne a syphilitic child. Her first question is 'Doctor why wasn t I warned?'

If the patient is unable to face alone the discussion with the marital partner the physician may often be of real aid. As a matter of fact, the average spouse wants accurate information as to infectiousness prognosis children etc which the physician can supply better than the patient, no matter how well he is instructed beforehand. Diplomacy tact, gentleness and kindness are essential. It is unnecessary and undesirable to discuss the lurid details of sexual indiscretions by which the patient may have been infected. The opportunities for extragenital infection are great stress may be laid on them.

Special circumstances of course arise on the basis of the spouse s personality of complicating physical or mental illness in the family of the character of the previous marital accord, and especially when the patient has early syphilis, in which disclosure of the diagnosis to the spouse may be undesirable. Each case must be decided on its individual merits but no circumstance obviates the absolute necessity of examination of the spouse.

Early syphilis discovered in a married person —There is no alternative to insistence upon examination of the marital partner to determine the presence or absence of conjugal infection. In the special circumstance of early syphilis which usually implies a recent sexual indiscretion it is sometimes desirable to arrange this without disclosure of the nature of the patient s illness. If the spouse is infected he or she must of course be told of the nature of the illness. *It is essential to remember that the investigation of the marital partner of a patient with early syphilis is not complete with a single negative examination.* The spouse may be in the incubation period of the disease at the time of examination and his or her freedom from infection cannot be determined without frequent physical survey and a bi-weekly serologic follow-up for a minimum of four months.

If the spouse is uninfected and if the patient will adopt the proper precautions as to intimate contacts, the tragedy of disclosure may be spared The precautions essential *to prevent infection of the uninfected partner* in such circumstances have already been discussed (Chapter III) —absolute avoidance of the intimate contacts of sexual intercourse or kissing for at least 6 months thereafter intercourse permitted if treatment is regularly and continuously carried on but limited to the periods of time during which the patient is receiving an arsenical preparation and with

the added protective use of a condom. If the condom is refused for one or another reason, the patient may copiously anoint the penis before intercourse with 33 per cent calomel ointment which serves as a prophylactic

Pregnancy should not be permitted until the patient, if the husband has fulfilled the criteria of "cure" of early syphilis i.e. prolonged continuous treatment (12–18 months) followed by a full year of probation without treatment with no lesions of syphilis and with frequently repeated negative serologic tests (Chapter XIII) or if the patient is the wife unless she is treated throughout pregnancy (Chapter XXVI) If and when an uninfected wife becomes pregnant no matter at what interval after her husband's infection her blood should be tested several times during the pregnancy and treatment administered if necessary

Late syphilis discovered in a married person —The necessity for examination of the spouse is as great as if the infection were recent. Here however a single examination, including physical survey serologic tests and if there are any neurologic abnormalities or if the original patient has neurosyphilis a study of the spinal fluid, is sufficient to determine the presence or absence of infection. If on examination, the spouse is found also to have syphilis, she must of course be treated. If no evidence of her infection can be discovered the question is at once asked, "What danger is there that she may acquire the disease in the future ? The risk of this possibility must be measured in terms of three factors—the duration of infection in the patient, the duration of the marriage and treatment. The relationship of duration of infection in the patient to this problem is more fully discussed presently under the heading of the eligibility for marriage of persons with late syphilis The duration of marriage is an equally important factor If the marriage is recent, the danger to the spouse cannot be accurately estimated the conditions under which infection may sometimes be transmitted by patients with late syphilis are too imperfectly understood. In these circumstances intimate contacts had better be restricted until the patient is thoroughly under the influence of antisyphilitic drugs. If on the other hand the couple has been married for some years and the wife (or husband) remains uninfected it may be reasonably assumed that there is no danger of future infection and no restrictions need be imposed Whether the date of marriage is recent or remote the treatment of the infected partner if conscientiously adhered to will practically eliminate all danger to the spouse

The question of pregnancy depends in part on whether the patient is husband or wife and in part on the economic factor Leaving aside the latter for a moment the man with late syphilis whose wife is normal may be permitted to have a child provided he has had at least 6 months of treatment before pregnancy is attempted and provided his wife's blood is tested frequently during pregnancy If the patient is a woman pregnancy may be allowed provided treatment is given throughout its course (Chapter XXVI) The economic issue however bulks large Is there any risk that the patient's disease will shorten life or impair earning power if so does the spouse understand this and are both partners willing and able to face the economic consequences which may arise? If the couple

has a clear understanding of this issue and if they wish to assume the risk, the physician is unwise to withhold his consent.

The Eligibility for Marriage of Syphilitic Patients

The unmarried man or woman with syphilis must not be allowed to regard his life as blighted so far as the possibility of subsequent marriage is concerned. In most instances he may sooner or later marry with every assurance for both spouse and children. Three factors enter into the question of marriage. These are —(1) the danger of infecting the spouse (2) the danger of the birth of syphilitic children (3) the danger that syphilis may incapacitate the patient or shorten his life, thereby adding to the economic hazards of marriage.

The danger of infecting the spouse depends in turn on two factors the duration of infection in the patient and the adequacy of antisyphilitic treatment. It is an old observation that for all practical purposes the infectiousness of syphilis even if untreated, diminishes with the passage of time, so that after five years the risk to others is small, even by such intimate contact as sexual intercourse. This is merely another way of saying that infection is usually transmitted by means of direct contact with the moist, treponeme-rich mucosal lesions of early syphilis (including the lesions of infectious relapse) In the main this observation still holds good, though there are occasional instances in which a man with syphilis of 10–20 years standing has infected his wife Certainly so far as eligibility for marriage is concerned any patient infected within 5 years should be regarded as having early syphilis and subjected to the same treatment restrictions.

For patients with early syphilis the requirements for marriage are that the patient shall have completed the equivalent of treatment outlined in Chapter XIII *and the subsequent year of probation.* If he has been treated continuously for 12–18 months, during the last year of which he has been seronegative if during the ensuing probationary year he remains seronegative and develops no lesions marriage may be freely permitted. Nothing less than this minimum should be tolerated however carelessly given assent to marriage may lead to terrible tragedies. If his early infection and treatment are complicated by such features as asymptomatic neurosyphilis treatment resistance or seroresistance, marriage had better be deferred until he has completed treatment and until a total period of 5 years from the date of infection has elapsed. During the last three of these years, he should have shown no evidence of infectious relapse.

If the infection is of longer standing than five years, the danger of infection to the spouse is probably eliminated completely by six months of continuous treatment and provided other conditions are fulfilled (see below) marriage may be permitted at any time. The statements in the last three paragraphs apply equally to men and women.

The danger of the birth of syphilitic children varies according to which partner has syphilis. If the infected individual is a woman the conscientious physician can never completely dismiss from his mind the possibility that if she becomes pregnant, her child may be infected. The considera

tions of duration of infection and of adequacy of antisyphilitic treatment just discussed though adequate for the protection of the spouse do not completely cover the contingency of pregnancy Nearly absolute safety for the child may be obtained however (1) if the mother is adequately treated before pregnancy (2) if regardless of her own status at the time of pregnancy she is treated continuously throughout its duration. In the light of the data of Chapter XXVI the latter requirement may be unnecessary until further evidence is forthcoming however the cautious physician will insist upon it

If the infected person is the man the possibility of the birth of a syphilitic child depends on his infectiousness for his wife. If she acquires syphilis from him the children may have syphilis if she remains uninfected, they will be free from it. The weight of evidence is so strongly against the possibility of the paternal transmission of infection that for all practical purposes it may be dismissed Not only will the children be free from syphilis if the mother remains uninfected, but there is also no danger of physical deformity imbecility etc. as a taint of syphilis There is no satisfactory evidence of any sort that syphilis damages the germ plasm The risk to the next generation is therefore entirely dependent on the factor of the potential infectiousness of the patient for his wife

The danger of incapacity or death from syphilis is a real one, more fully discussed in Chapter III It is manifestly unfair for the syphilitic patient to expect his fiancée to accept this risk blindfold. If the patient s life is shortened or if after marriage and the birth of several children he becomes a bedridden invalid from cardiovascular or neurosyphilis an economic tragedy may be precipitated. Marriage is a partnership the hazards as well as the pleasures of which should be faced by both partners equally For this reason if for no other no person who has acquired syphilis should contemplate marriage without a frank disclosure to his or her intended spouse of the fact that he or she has had syphilis and this announcement should be supplemented by a conference between both parties and the physician in which the possibilities of the future are frankly set forth. Many factors require consideration i.e. the earning capacity of the husband his protection by life insurance the ability of the wife to earn her own living if necessary the possibility of financial security and in security If the danger of infection is eliminated and if they choose to take the economic risk after full explanation the physician need not object, even though his patient has tabes paresis or aneurysm.

The reader will have noted that we lay no stress whatever on whether the candidate for marriage has a positive or negative blood or spinal fluid examination nor even on his physical status except insofar as this may involve the risk of infecting others. These are considerations which do not concern the physician whose only duty is to safeguard uninfected persons adult or as yet unborn against infection and so far as possible to safeguard society from the possibility of having to support the indigent family of an incapacitated or prematurely dead patient.

When a patient with early or late syphilis has married with the physician s consent on the basis outlined above pregnancy may also be per

mitted with the sole restriction that the mother's blood be tested every 4–6 weeks during her pregnancy Treatment is to be given at once if necessary

While the physician should advise any syphilitic person contemplating marriage to tell his fiancée of the situation he is justified in bringing extreme pressure to bear in one special circumstance A patient with early syphilis who insists on marrying without consent before his treatment and probationary year are completed should be told that if he persists, the local Health Department will be notified and requested to quarantine him forcibly until he is presumably non-infectious.

The desirability of attaching to consent to marriage the condition of premarital discussion with the fiancée rests on several grounds in addition to the economic one already discussed. First no physician can provide an absolute guarantee to any patient that infection will not be transmitted in the marital relationship The chance may with proper precautions be infinitesimal, but it exists, and the fiancée must be given the opportunity to accept or refuse it.* Next it is difficult properly to protect the child in a possible pregnancy unless the mother knows the situation in advance. Third the possibility that the marriage will be broken up by divorce is great if the fact of the patient's infection concealed before is brought to light accidentally after marriage. And finally the person who in the last analysis is better able than the physician to judge the desirability of marriage for a syphilitic patient is the individual whom that patient wants to marry, provided all the facts are freely supplied.

Compulsory premarital examinations for syphilis[f]—The arguments for and against these laws have been summarized by Moore.

In favor of them are

1 They are valuable methods of case finding, the first essential of any syphilis control program.

2. They will decrease the transmission of syphilis in marriage.

3. They will decrease the incidence of congenital syphilis.

4 By insistence on blood tests by "approved laboratories" they will raise the standard of laboratory performance throughout the country

5 They will have a general educational value, in keeping the problem of syphilis clearly in the public mind

The arguments against them, equally briefly are

1. In the diagnosis of syphilis, emphasis is laid almost wholly on the laboratory

2. The specificity of serologic tests for syphilis in the best of hands (the originators of the tests themselves) is technically short of perfect. The recent serologic surveys of the United States Public Health Service and the American Society of Clinical Pathologists point out that (a) in the most competent hands (those of the originators) modern serologic tests provide from 0.2 to 1 per cent technical false positive results in known non-syphilitic persons (b) in labora

* The physician must safeguard himself in this respect also. If a patient marries with consent, but without telling his fiancée that he has had syphilis, and if she subsequently becomes infected, the physician lays himself open not only to unpleasant recriminations but to legal proceedings as well.

tories other than those of the originators performance may be as good as this but an important number of laboratories (including more than one state or municipal health department laboratory) report technical false positive results in normal persons in from 1 to 10 per cent of those tested.

3 The specificity of serologic tests for syphilis is not only technically but also biologically short of perfection. Several diseases including two reasonably prevalent in this country (malaria and infectious mononucleosis) cause biologic false positive results in a significant proportion of cases and far too little positive modern information is available as to biologic false positive tests in many other conditions (e.g., vaccinia, after serum treatment, during fever or jaundice etc.)

Moreover evidence is accumulating to suggest that the blood of a small but as yet unknown proportion of perfectly normal persons may from time to time or permanently contain enough reagin or reagin-like substance to cause a transitory or permanent biologic false positive serologic test.

Therefore in view of the second and third items a considerable number of non-syphilitic persons will be caused undue alarm delay in marriage and expense in unraveling the significance of false positive or doubtful results. The case reports of Stokes and Ingraham make clear that this is already happening, as other consulting syphilologists also can testify

4. The blood test is a wholly invalid indicator of infectiousness or non-infectiousness in syphilis.

5 Four states (Wisconsin, Illinois Michigan and Kentucky) have rushed so headlong into such legislation as to forbid the marriage of a person with a positive serologic test for syphilis at any time, regardless of his actual or potential infectiousness Their hasty misguided and unjust legislative example may be followed by other states.

6. Where the law requires blood test evidence to be reinforced by clinical examination, it is even more faulty since, at an estimate 95 per cent of all patients infected with syphilis will show no gross physical evidence of the disease at the time of life when marriage is usually contracted.

7 The law will not serve its purpose in preventing the spread of syphilis within marriage. Premarital intercourse is already so frequent as to make the law an effort to lock the stable door after the horse is stolen. In the social and economic groups having the highest incidence of syphilis the incidence of common-law marriages and of illegitimacy will be increased.

For the interested reader the situation to date (1941) has been summarized by Snow Nelson, Stokes and Ingraham and Kolmer

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Chapter XXXI

THE PROPHYLAXIS OF SYPHILIS

Syphilis is almost if not quite, a completely preventable disease. There are three methods of prophylaxis, each of them satisfactory to some extent and under certain conditions. These methods are

1 Mechanical which aims at the prevention of contact of a normal mucous surface with one containing infectious lesions.

2 Chemical which aims at the destruction of treponemes on the skin or mucosal surface before their penetration into deeper tissues.

3 Chemotherapeutic, which aims at the destruction of treponemes which may already have penetrated through surface to deeper tissues.

Mechanical Prophylaxis

The Condom —The rubber sheath or condom is the most readily available and in many ways the most satisfactory of all prophylactic methods. It is the only method which offers simultaneous protection to both sexes and against not only syphilis but other venereal diseases as well. Condoms are easily obtained everywhere (fortunately pharmacists' associations have not been generally successful in their efforts to restrict their sale to drug stores and they may usually be purchased at gasoline filling stations, from hotel bellboys, night club attendants, etc.) They are relatively inexpensive though their retail price provides an unduly large margin of profit over manufacturers' cost and in the interest of the public health they should certainly be cheaper

The condom is easily applied by the man himself its use involves no discomfort and it does not seriously interfere with sexual pleasure. Adjusted before intercourse it involves none of the psychological hazards and inconveniences associated with other prophylactic methods.

There are however certain disadvantages to the use of condoms. There is no protection from infection during preliminary sexual play before the sheath is adjusted nor against infection of or from the pubic area, thighs and scrotum. Both syphilis and gonorrhea, and perhaps other venereal diseases may be contracted from contact with infectious material on the outside of a condom recently used. The greatest risk is of course from breakage or leakage of the condom itself due either to its poor quality to its improper adjustment, or to the rapid deterioration of its thin rubber walls from prolonged contact with an oil lubricant (mineral oil vaseline, etc.)

For many years the defective quality of condoms was the greatest objection to their use in prophylaxis. Recently however standards have been set for the manufacture of these products by the United States Food and Drug Administration and those sold in interstate commerce are carefully supervised. Samples bought in the open market are subjected to

careful tests and defective products are confiscated. As a result of this governmental supervision incompetent manufacturers have been largely driven out of business and the product of the few remaining large manufacturers is approximately 95 per cent satisfactory both as to gross and pinhole defects

Certainly the medical profession should lend every support to improving the standards of manufacture of condoms and to widening their distribution The extent to which already they are of value in the prevention of venereal disease, especially syphilis may be guessed at from the fact that more than 400 000 000 are sold in this country yearly (Warren)

Chemical Prophylaxis

The uniform application of chemical prophylaxis could this proceeding be carried out would reduce the incidence of syphilis enormously We owe the experimental proof of the efficacy of chemical prophylaxis with 33 per cent calomel ointment* to Metchnikoff and Roux. Its use in our own Army and Navy as well as in those of others before and during the World War furnished a convincing clinical demonstration on a vast scale Its use is based on the fact that every sexual exposure is a potential source of infection and that if proper prophylactic measures can be applied before organisms have had time to penetrate the tissues, not only syphilis but also (by other means) gonorrhea and chancroid as well, may be prevented Prophylaxis is most effective if applied within the first hour after exposure (the first exposure not the last of an all-night session) and rapidly decreases in value as the interval between exposure and treatment lengthens. Against syphilis it is perhaps still of some value as late as 8 hours after exposure. Incidentally this fact suggests that spread of treponemes from the site of inoculation to the neighboring lymph nodes is not as rapid in man as under the artificial conditions of forcible injection of the virus in animals Within these time limits prophylaxis fails to protect in only about 0.3 per cent of the instances in which it is used (Ashburn Riggs Moore, Walker)

Experience during the World War and since has however clearly demonstrated one tragic fact. Although chemical prophylaxis is effective it is utilizable only under conditions of military or semi-military control. Men will not avail themselves of this procedure unless forced to so so by fear of punishment. Even in the Army when the acquisition of a venereal disease after an exposure without prophylaxis formerly meant court martial and additional penalties many soldiers preferred to run the risk of infection To the physician with Army experience the contrast between conditions of military and civil life are discouraging in the extreme. During World War I one of us (Moore) had under his immediate charge some 75 prophylactic stations giving more than 100 000 treatments a year In the ensuing 23 years of civil life, in private practice and in one of the largest syphilis clinics in the country he has seen two applicants for prophylaxis both of these privately and none in the clinic Kemp in a clinic equally

* No more satisfactory substitute has been discovered.

large and one which continually brings to the public's attention the dangers of venereal disease has had only 500 applications for prophylaxis, all from males during the past eight years.

The inapplicability of prophylaxis to civil life does not rest on moral grounds. The establishment of prophylactic stations for civilians has been opposed by religious bodies, reformers and uplifters on the grounds that this step would countenance and encourage sexual promiscuity. The breath wasted on such objections might just as well have been saved. The project fails not for the reasons just mentioned not from indifference and certainly not from ignorance since the last World War left us with some 4,000,000 men adequately instructed about prophylaxis but simply because prophylactic stations are not practical. Warren has succintly put the reasons why if available they would not be used. They are

1. Inconvenience. People will not travel to a station within one to three hours after exposure, especially at night.
2. Fear of publicity. Exposed persons will take a chance rather than register or be seen at a station by friends, private detectives, or blackmailers.
3. Fear of embarrassment. Imagine the meeting of two persons at a prophylactic station after an affectionate parting an hour before!
4. Lack of compulsion. There is nothing to compel a civilian to visit a station.

It seems to us that, though every physician ought to be familiar with methods of prophylaxis and prepared to apply them if requested the only hope for the large scale application of the method to the reduction of venereal disease incidence lies in its continued use in the Army and Navy and its general introduction into the field of industrial medicine. This is an ever widening form of medical practice. Increasingly large numbers of industrial corporations are with the help of their own medical departments considering the relationships of disease to efficiency in industry. It is possibly practicable for such medical organizations to make available prophylaxis to their firms employees. Could this plan be largely or universally adopted by industrial medicine a material reduction in venereal disease incidence in the general population of the country might be apparent within a few years.

Technique of prophylaxis for the male *

If possible do not allow the patient to administer the treatment to himself. The patient is made to urinate. He is provided with a basin of warm water and gauze wipe with which he washes the genitals thoroughly while liquid green soap is dropped on the penis. The washing to be done thoroughly should consume about 5 minutes and should include the penis, scrotum pubis, and the adjacent areas of the thighs. Use especial care to wash thoroughly the folds of the frenum and foreskin. After washing, the parts should be dried thoroughly. The washing with soap and water is important soap is the only part of the treatment effective against chancroid, and is also of value as a destroyer of the organism of syphilis. Before proceeding further the presence of urethral discharge or genital sores is noted.

The next step is the injection of 1 dram (4 cc.) of a freshly made up 2 per cent protargol solution (or a 10 per cent solution of argyrol) into the urethra by the

* From Moore, Cole, Schamberg, Solomon, Wile and Stokes.

physician. The patient then holds the meatus firmly between the thumb and forefinger for five minutes, from time to time allowing a drop to escape from the meatus so that all parts of the urethra are in contact with the solution. At the end of five minutes the protargol is allowed to escape, without pressure or stripping, so that a few drops remain. One-half to 1 dram (2 to 4 grams) of 33 per cent calomel ointment is next rubbed thoroughly by the patient, under the observation of the physician into all parts of the penis for five minutes, special attention being paid to the retracted prepuce the frenum, and the glans The scrotum also should be rubbed with ointment. The genitalia are then wrapped in toilet paper or waxed paper to protect the clothes and the patient is instructed not to urinate for four or five hours.

The formulae for calomel ointment used in the United States Army and Navy which have proved their efficacy are as follows

United States Army	Parts	United States Navy	Parts
Hydrargyri chloridum mite	30	Calomel	33
Adeps benzoinatus	65	Camphor	2
Cera alba U.S P	5	Phenol	3
		Anhyd. lanolin	39
		Benz. lard	20
		Beeswax	3

Remember that soap and water is protection against chancroid and partially against syphilis, protargol against gonorrhea, and calomel ointment probably only against syphilis.

Before and since the war an extensive search has been made for one drug or a combination which might prove effective against all three diseases, but so far without satisfactory results.

Theoretically prophylaxis should be equally applicable to the female Practically we know of only a few instances during the first War in France or here at home in which the request was ever made This is probably due in large part to ignorance on the part of women or failing that, to embarrassment and shame. If the necessity for early treatment in the female occurs as for example in case of rape the technique is as follows

Technique of prophylaxis in the female †

Have the patient urinate Place the patient in the lithotomy position Wash the genitals and adjacent parts with soap and water Give a douche of 2 quarts of sterile water temperature 100°F., followed by 2 quarts of 1–2000 mercuric chlorid solution, and wash external parts with the latter Dry the vagina and vulva by sponging. Swab the entire vagina, through a speculum with a 2 per cent protargol solution, or 10 per cent argyrol solution, freshly made reach every fold and especially the posterior vault and external os. Swab the entire vulva in the same way reaching every recess and endeavoring to facilitate the entrance of the solution into the openings of Skene s ducts and Bartholin s glands. Inject enough of the same solution into the urethra to distend it moderately and let the patient hold her finger (in a rubber glove) against the meatus to retain the solution for from three to five minutes.

Such combinations are offered for sale in single treatment collapsible tubes by several manufacturers, under various trade names There is no exact knowledge as to their efficacy but certainly if nothing else is available to the exposed person they should be tried

† From Moore, Cole, Schamberg, Solomon, Wile and Stokes.

Douche the vagina and vulva with a small amount of sterile water and sponge dry with gauze. Apply calomel ointment to the cervix, vagina, vulva, and adjacent parts, rubbing thoroughly into the recesses and folds of the mucous membranes and skin, and taking at least 10 minutes for the operation. Do not use more than 4 grams (1 dram) of calomel ointment in the vagina. Cover the external parts with oiled silk or waxed paper securely and instruct the patient to allow ointment to remain for several hours before washing the parts.

Technique of prophylaxis in physician or nurse—Unfortunately extragenital chancres on the fingers of physicians and nurses are only too common. Laryngologists, obstetricians gynecologists and dentists are the chief sufferers. Usually these are due to sheer carelessness the handling of syphilitic lesions with bare hands and failure to use ordinary cleanliness afterwards. Soap and water if immediately and thoroughly applied to the hands is adequate and complete prophylaxis against infection of this sort. This has been experimentally confirmed by Walker If abrasions are present on the fingers especially about the nails 33 per cent calomel ointment should be thoroughly rubbed into the hands after washing.

More dangerous are puncture wounds from an infected needle or instrument recently used on a patient recently infected with syphilis. Here soap and water cleanliness does not suffice, nor does the local application of such antiseptics as alcohol, iodine mercurochrome bichloride of mercury etc. The organisms if present on the instrument, have been introduced deeply beneath the skin and will not be reached by external applications Under these circumstances, the puncture wound should be laid open to its approximate depth with a sharp scalpel allowed to bleed freely and the incised wound packed with 33 per cent calomel ointment which remains for 24 hours. This method has been uniformly successful in a dozen or so cases in which we know it to have been used. Since organisms disappear from the blood stream completely so far as we know after the establishment of latency similar wounds acquired in treating a patient with late syphilis (of more than 4 years' duration) are much less dangerous to the operator

If the physician or laboratory technician gets blood from an infectious patient in his mouth as in pipetting blood or if such a patient coughs droplets into the face or open mouth of the physician soap and water should be used at once. For further security if desired calomel ointment may be applied after thorough drying of the buccal mucosa.

Should a patient with moist lesions in his mouth cough droplet material into the physician's eye, the conjunctival sac should be copiously irrigated at once with normal saline solution five per cent argyrol may be dropped into the eye though its value is questionable. Other antiseptics must be avoided because of their irritant effect on the external coats of the eye.*

In the event of definite exposure by puncture wounds or by the deposit of moist material on mucous surfaces of mouth or conjunctiva, the physician or nurse will do well to adopt an attitude of watchful waiting to-

* Chancre of the conjunctiva is sufficiently rare that we have seen only two cases which occurred in individuals who were neither physician nor nurse.

gether with bi-weekly serologic testing for three months following the accident.

The mechanism of chemical prophylaxis.—So far as syphilis is concerned, it is possible that the only portion of the chemical prophylactic ritual outlined above which actually fulfills its purpose of destruction of treponemes still on the *surface* of the skin or mucosae is immediate washing with soap and water. By an ingenious experiment, Mahoney has demonstrated that rabbits inoculated with syphilis may be protected against infection by the application of calomel ointment not to the inoculated site but elsewhere on the skin. What has been regarded as chemical prophylaxis with local destruction of surface organisms may after all be chemotherapeutic prophylaxis with the destruction of treponemes actually in the tissues by a spirochetícidal drug (in this case mercury) circulating in the blood stream.

Chemotherapeutic Prophylaxis

Arsphenamine prophylaxis.—Some experimental work has been done (Greenbaum and Harkins, Wakerlin and Loevenhart, Probey) on the prophylactic action of the arsphenamines in experimental rabbit syphilis. Animals have been inoculated with syphilis, usually by intratesticular injection of virus, and treated at intervals thereafter ranging from 1–48 hours with single or multiple injections of an arsphenamine. There is general agreement that under these conditions a single dose of 15 mgm/kg of arsphenamine or 20 mgm/kg of neoarsphenamine will protect the animal against infection. These doses are 25–30 per cent greater than the minimum curative single dose in established early infections.

It has been variously proposed here and abroad that arsphenamine be used as prophylaxis in potential infections in human beings. Cases have been reported in which the patient, having been exposed within the preceding 48 hours to an individual with known infectious lesions, has been treated with one or several injections of arsphenamine, has failed to develop lesions of syphilis, and has maintained a persistently negative serologic test. The argument is used that since seronegative primary syphilis may be successfully managed with less treatment than is necessary after the development of secondary lesions, still less treatment should be needed if it can be started shortly after the moment of infection and before the appearance of a chancre.

Personally we object strongly to this procedure. Its advocates have not as yet proved their point. Animal experiments may not be cited as proof. In rabbits, the prophylactic dose is one-third greater than the single curative dose. Since curative experiments in rabbits are not directly translatable to human beings (although a single dose of 10 mgm/kg of arsphenamine will "cure" 90 per cent of rabbits with early infections, less than 10 per cent of human beings with equally early infections will be "cured" by similar treatment) it is reasonable to assume that too strict an analogy in prophylactic experiments is unwise. In man, the effect of prophylactic treatment, whether with one or several injections of an arsphenamine, may only suppress and not eradicate the infection. Though

such a patient may remain free of lesions and seronegative for years he may subsequently develop grave late lesions involving nervous system or cardiovascular apparatus

Furthermore if prophylactic treatment is given both physician and patient are in the unfortunate position of not knowing if the patient would have escaped infection provided nothing had been done. There is the responsibility of giving a potentially toxic drug which may cause incapacitating illness or even death to a patient who may not need it. There is the constant subsequent uncertainty in the minds of both physician and patient as to whether or not the patient ever had syphilis and the constant fear of possible recurrence which hangs like a sword of Damocles over the patient s head.

It seems to us that in view of all these uncertainties it is better for the exposed individual to keep himself under constant observation reporting for darkfield examination at the first appearance of any suspicious lesion, than to adopt arsphenamine prophylaxis. The period of observation should cover at least 3 months after the suspicious exposure and during it repeated blood tests should be done at weekly or bi-weekly intervals The chance of escape from infection is considerable the prospect of radical cure" if evidences of infection develop excellent.

Under all ordinary circumstances we do not believe in administering antisyphilitic treatment, except as a therapeutic test in suspected late syphilis, until the diagnosis of syphilis is proved

There is however one exceptional case in which our personal aversion to arsphenamine prophylaxis (or better phrased to early arsphenamine treatment) has been overcome. This is the situation of which we have now seen several examples, of a pregnant woman who has been once or repeatedly sexually exposed to a man with darkfield positive penile lesions In such cases we have started arsphenamine at once, even though there was no clinical or laboratory evidence of infection on the basis of the near certainty of infection, the possibility that all evidence of it might be suppressed by the pregnancy (cf Chapter XXVI) and the risk to the fetus.

It is only fair to point out that there are thoroughly competent workers including some of our own associates, who disagree with this point of view Their attitude is well summarized by Morgan. In the long view perhaps the decision is best made on the probability of syphilophobia in the patient *and the procedure adopted which provides the lesser risk of this serious psychiatric disorder*

Occasionally one meets a patient whose reading has been sufficiently catholic to include the subject of arsphenamine prophylaxis and who insists on its use. To such a one we believe that the situation should be explained and the responsibility shifted to the patient s shoulders. The physician may well say — Since you have been exposed to a known infectious syphilitic it is possible though not certain that you have acquired the disease If you decide to accept this as a certainty rather than as a possibility you must regard yourself as a syphilitic and though you are more fortunate than most in that your treatment is begun very early

you must be followed for a lifetime of observation exactly as if you had developed lesions.

If the patient chooses prophylactic treatment (1) it should in our opinion consist of not one or two arsphenamine injections but of at least one complete arsphenamine course (8 arsphenamine or 10 neo- or silver arsphenamine) followed by a course of bismuth (2) the patient should be followed with monthly serologic tests for the first year every 2 or 3 months for the second year and thereafter every 6 to 12 months as long as he lives (3) periodic physical examinations should be done at yearly intervals and (4) he must have at least one negative spinal fluid examination at the end of the second year of observation. This is essential to guard against the possibility that the infection has been only suppressed instead of eradicated with the resultant possibility of cardiovascular visceral or neurosyphilis in the future Even the worst syphilophobe may well hesitate at all this if he is unwilling to subscribe to it especially the probationary follow-up it is far better to withhold prophylactic arsphenamine and to observe him closely for the appearance of lesions or the development of a positive serologic test before instituting treatment.

The stovarsol or spirocid prophylaxis of syphilis —French and German medical periodicals have carried advertisements of the prophylactic efficacy of this drug, marketed in America as stovarsol or acetarsone. It is a pentavalent arsenical which may be given by mouth The pleasing implication is that a man may cohabit with known syphilitic women provided only he is thoughtful enough to provide himself with a few spirocid or stovarsol tablets which he swallows before and after intercourse. Aside from the repulsive implications of this sort of medical publicity the scientific work on which the implications are based is of the most shadowy variety The experimental data are conflicting and the work done in our own laboratory (Poole) indicates that the effective prophylactic or curative dose of stovarsol is very close to the toxic dose. The method is not advised

The bismuth prophylaxis of syphilis —Kolle has shown that in experimental animals the intramuscular injection of insoluble bismuth salts before or shortly after inoculation with syphilis will protect against the development of infection. Levaditi unable to confirm Kolle s findings with insoluble bismuth salts nevertheless demonstrated experimentally that liposoluble salts injected intramuscularly afforded complete protection against syphilis These facts have been utilized clinically by Sonnenberg who for nine years practiced bismuth prophylaxis among supposedly non-syphilitic prostitutes by injecting them bi weekly with 2.5 cc of a 10 per cent suspension of bismuth subnitrate in oil. During this time only 37 of 327 prostitutes so treated acquired syphilis and in every instance before the fourteenth injection Sonnenberg feels that this is absolute proof of the efficiency of his plan. However the method can hardly be of practical value in the control of syphilis since for obvious reasons it is not applicable to the population as a whole nor even to prostitutes unless they are under enforced medical supervision In addition all the arguments

against arsphenamine prophylaxis may be advanced against this form of bismuth prophylaxis. Hanzlik has recently shown that rabbits may be protected against infection with syphilis by prolonged drinking of sobisminol solution before and after inoculation and suggests that the oral use of this drug may be applicable to the prophylaxis of syphilis in man. So far however the method has not been clinically tried.

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CHAPTER XXXII

THE PUBLIC HEALTH ASPECTS OF THE TREATMENT OF SYPHILIS*

IN its relation to the public health, syphilis may aptly be regarded as two diseases one of which, early syphilis is infectious and like tuberculosis and other infectious diseases requires the attention of public health officers to diminish or prevent its spread the other late syphilis, is not a major problem because of infectiousness but like cancer demands the attention of public health officers because of the high incidence of incapacitating disease and death which it causes.

Treatment and the control of syphilis —Treatment facilities at present available in the United States are not adequate for the control of syphilitic infection. In the discussion of this topic it is profitable to start with a definition of terms. What is meant, precisely by the phrases "adequate treatment facilities" and "the control of syphilis"? As to the former does "adequate" mean adequate to meet the present demand or adequate for the potential demand? As to the latter it may perhaps be agreed that the control of syphilis means essentially the same thing as the control of small pox or any other infectious disease i.e its virtual eradication.

It may also be assumed that if treatment facilities were adequate the control of syphilis would be aided. This is perhaps more nearly fact than assumption. As to early syphilis it is agreed that the spread of infection can be best prevented not by reformation of the sex morals of a nation nor by the forcible isolation of infectious persons but by the early use of the arsphenamines. A single dose of one of these drugs provides a method of destroying surface organisms in a few hours, of healing infectious lesions in a few days and of abolishing infectiousness with a rapidity not equaled by any method in any other infectious disease. It is however true that one or a few doses will not accomplish the permanent abolition of infectiousness, and that indeed to stop with one or a few doses may actually increase the incidence of infectious relapse over that to be expected if no treatment at all is given. To prevent fresh lesions from appearing to reduce the incidence of infectious relapse to a minimum of 2 per cent or less at least twenty injections of an arsphenamine plus an equivalent amount of heavy metal, given by the continuous system are necessary From the public health standpoint, it seems obvious that if it were possible promptly to recognize every individual freshly infected with syphilis and to administer this minimum of forty weeks of treatment the spread of syphilitic infection would be immediately and enormously reduced.

* We are indebted to Dr R. A. Vonderlehr Assistant Surgeon General, Division of Venereal Diseases, United States Public Health Service, for his courtesy in reviewing this chapter and in providing current statistical information.

As to late syphilis it is agreed that most forms of the disease are amenable to symptomatic relief and that progression or relapse may be prevented in the vast majority of cases if the proper form of treatment can be given over a long enough period of time It seems further obvious therefore that if it were possible to recognize all individuals with late syphilis and to administer the optimum amount of treatment, incapacity and death and the economic loss resulting therefrom could also be immediately and enormously reduced.

The incidence of syphilis in the United States —Whether early and late syphilis are being recognized to the maximum degree possible and whether when recognized they are being treated by proper methods and for the optimum length of time are points closely related to a discussion of treatment facilities adequate to meet the actual or potential demand.

It is extremely difficult to establish adequate estimates of the annual incidence of syphilis in the United States Data published by the U S Public Health Service based on surveys of licensed treatment sources conducted in 1936 and 1937 are no longer suitable as indices of the present status of the problem Perhaps the best information available today is contained in the reports of the State Health Departments to the Surgeon General These reports indicate that during the fiscal years 1939 and 1940 a total of approximately one-half million cases of syphilis were recorded as having sought treatment from private physicians and clinics presumably for the first time since onset of infection. According to estimates based on 1940 reports, approximately 40 per cent of these cases sought treatment during the early stages of syphilis i.e. within the first 4 years and only one-half of these (or 20 per cent of the total) were treated during the primary-secondary stages of the disease.

The minimum annual attack rate for syphilis may be obtained from these recorded cases of primary-secondary syphilis, since it is a safe assumption that none of those infections was of more than a year's duration upon seeking treatment On this basis therefore the minimum annual attack rate for syphilis without corrections for race age or sex would be approximately 75 per 100 000 population in the United States. It is recognized of course that such a rate represents only the cases reported as seeking medical care and that reporting practices especially among private physicians, are far from complete In addition such a rate would not measure the large proportion of persons with fresh syphilitic infections who for reasons of ignorance or apathy never seek medical care or wait to seek such treatment until the disastrous effects of late syphilis become symptomatic

Since from the public health standpoint we are more interested in early than in late cases it is pertinent to ask Do all patients with early syphilis seek medical attention competent to abolish infectiousness? If not what proportion do seek such competent care and what happens to the remainder?

A definitive answer in exact terms cannot be given to these two question but such information as is reported by State Health Departments supports the theory that more than half the persons freshly infected with

syphilis do not seek competent medical attention during the early and infectious stages of their illness. Two important reasons for this failure exist. First is the fact that early syphilis is sometimes perhaps often, symptomless i.e. the primary and secondary lesions are either completely lacking or so trivial and evanescent as to escape attention. How often this occurs in human beings is unknown and for various reasons is probably impossible of exact determination Obviously however a patient who does not realize that he is ill does not consult a physician. Second, the American Social Hygiene Association has found that annually more than twice as many individuals sought treatment for venereal disease across drug store counters as came to qualified medical sources in such cities as San Francisco California, Birmingham Alabama, Dallas Texas and New Orleans, Louisiana. When casually asked what one should do if infected with a venereal disease, less than one-half of the young men so questioned advised going to a clinic or to a medical practitioner for treatment the remainder suggested some improper type of treatment either self-treatment or that obtainable from the advertising quack or drug store and in some instances advocated that no treatment be sought, stating that the lesion would heal of its own accord.

It may be assumed, therefore that if instead of the present annual treatment demand from freshly infected patients all persons with syphilis in the very earliest stage came without delay to treatment from recognized medical agencies, the present case-load could easily be quadrupled.

What of patients with late syphilis? Why do so many patients delay applying *for treatment until they have developed late syphilis? Is the* annual crop of such patients the maximum possible number who could be brought under treatment? The reasons for the delay in applying for treatment are given in the last paragraph—symptomless infection treatment for early syphilis lacking because the disease was unrecognized or inadequate because self-administered or given by improper medical agencies

The actual reported demand for treatment of some 400 000 new patients with late syphilis annually is far below the potential demand that would result from an organized effort to bring all syphilitics under treatment.

Case Finding

Organized case finding, a procedure familiar for years to public health officials and clinicians interested in tuberculosis, is apparently a relatively new idea in syphilis or at least one that is only beginning to receive general application. Two important methods are available routine serologic testing, and the epidemiologic search for infected contacts of patients with syphilis.

Routine serologic testing of persons applying for medical care —The first and most obvious step in syphilis case finding is the application of routine serologic testing to increasing numbers of patients applying to hospitals or practitioners for medical attention. For years, most good hospitals have employed routine tests on some services (e.g., for all medical or obstetrical in-patients) recently a few hospitals including our own, demand routine tests on all patients admitted to any service in-patient

or out patient, for any complaint. Private practitioners have been slower to adopt this procedure but in recent years are doing so in encouragingly increasing numbers.

To introduce the serologic test for syphilis as a routine in every department of all hospitals is perhaps an unobtainable counsel of perfection yet it has been nearly completely accomplished in one field of medicine i.e. obstetrics in which Exner reports that 93 per cent of 268 representative antepartum clinics examine every pregnant woman for syphilis by this method If it is possible here with the aim of eradication of congenital syphilis by the treatment of infected women certainly it should be possible in other branches of medicine with the aim of prevention of infection of the woman!

To what extent would the spread of syphilis be reduced if this method of case finding could be employed universally in persons applying to hospitals for aid to say nothing of those coming to physicians offices? The cases recognised over and above those diagnosable clinically would be (1) those patients with early syphilis in whom the infection had been symptomless or in whom the lesions had been unrecognized or misinterpreted by the examiner (2) the large class of those with latent syphilis i.e with no clinical evidence of the disease and (3) those with late syphilis whose lesions had been overlooked or misinterpreted In our own clinic these three classes make up 44 per cent of all admissions.

Routine serologic testing of healthy persons in selected population groups—Since the development of an organized syphilis control effort, much attention has been devoted to serologic surveys of certain selected population groups of healthy persons e.g in industry in colleges in enrollees of U S. Army and Navy etc This too is a valuable method of case finding, but it is subject to several possible abuses.

First there is danger that certain occupational groups will be unjustly singled out on the ground of their potential infectiousness for others For example there is no adequate reason for stigmatizing as especially dangerous to the public from the standpoint of syphilis the occupational groups of food handlers barbers and beauty parlor operators The risk that a syphilitic individual in any one of these groups will transmit his infection to others *accidentally and by virtue of his occupation* is almost infinitesimally small. That he may spread infection by sexual intercourse or kissing, of course is probable but so may the syphilitic steel worker office worker or plumber If it is desired to search for syphilis among healthy workers in industry the invidious selection of these occupational groups only is unjustified.

Second and even more important, there is danger that the discovery of a positive blood test in a potential or actual employee will lead to refusal of employment or discharge This unfortunate policy has already been adopted by certain unenlightened industrial corporations and even by the United States Civil Service Commission on the triple ground of danger of transmission of disease of an increased accident rate or increased industrial compensation hazard. Only the two latter of these arguments require comment, since the risk of transmission of syphilis in industry is practically non-existent.

Syphilis in industry.—The risk that a syphilitic person handling dangerous machinery may endanger the lives of others is, for all practical purposes, limited to patients with cardiovascular or with neurosyphilis and more particularly to those with paresis. There is not the slightest evidence to indicate that industrial accidents are more frequently due to the carelessness of syphilitic persons (excluding the two classes named) than to that of non-syphilitic workers. The routine positive blood test does not establish the diagnosis of cardiovascular or neurosyphilis. These diagnoses can be reached only after complete study of the patient.

It is not intended to suggest that persons with syphilitic heart disease who may suddenly drop dead or those with paresis, whose judgment is vitally impaired should be placed in charge of hazardous machinery which may endanger the lives of others as well as their own. It is a curious fact, however that the industrial corporations most likely to suffer from serious accidents due to syphilis, e.g. railroads, aviation companies, bus and trucking companies, taxicab companies, do not for the most part require even routine serologic tests on employment and, so far as is known, railroad engineers switchmen train despatchers and aviators—all persons responsible for the lives of tens or hundreds of others—are in few if any companies required to submit to yearly periodic routine tests. Obviously it does not protect the public safety to employ non-syphilitic engineers or aviators unless steps are taken to assure that these individuals remain non-syphilitic during the period of hazardous occupation.

From the point of view of public safety therefore, the routine serologic test is not as yet in proper general use by the corporations most responsible for the protection of others and, where it is used this use is for the most part unintelligent. A routine positive test should not be the criterion for refusal to hire or dismissal on this ground. It should, however if hazardous occupation is involved be the signal for careful individual decision in each case. If cardiovascular or neurosyphilis can be excluded employment should be granted or continued provided adequate treatment has been or can be given.

In non-hazardous occupations the routine positive serologic test of course deserves no consideration from the standpoint of public safety

The additional economic risk imposed upon the company by industrial compensation or other forms of social insurance is the greatest objection to the employment of syphilitic persons In this field the sweeping decision not to employ or to dismiss syphilitic individuals is based on inadequate information or if particular corporations do have adequate data covering the point these data have not been made freely available in medical literature.

So far as is known there is (except in rare instances) no good evidence to indicate that a syphilitic worker *who does not have cardiovascular or neuraxis involvement* is any more likely (a) to be involved in accidents than his non-syphilitic brother or (b) if involved in an accident, to suffer any more serious or prolonged disability or (c) to suffer more severely from intercurrent non-syphilitic disease or even (d) to undergo material shortening of his life span. Whatever risk there may be of any of these

eventualities may be largely guarded against (except in cardiovascular or neurosyphilis) by adequate treatment.

The employer who knows that his employee has syphilis is in a position to ensure the adequacy of treatment if the patient remains in his employ but if he refuses to hire or dismisses such persons any form of control over treatment except that imposed by the patient himself is lost.

The procedure by which an employer can best protect himself against possible loss from syphilis and at the same time best serve society is not therefore wholesale refusal to employ syphilitic workers but individualization in each particular case.

Our attitude toward *compulsory* pre-marital and pre-natal blood testing is expressed in Chapter XXX.

Case finding by the epidemiologic approach —With another important method of case finding the public health officer is even more directly concerned namely the epidemiologic investigation of contacts and families of infected persons. This method of approach so familiar in other infections is equally applicable to syphilis Only by its use can one detect the ignorant, careless or vicious person who though infected escapes routine serologic testing because he does not consult any medical agency for advice. The practitioner's responsibility in this direction has been repeatedly emphasized throughout this book. Our own experience with the method has been reported by Turner and (in children) by Dyar and Goodwin.

Organized case finding by routine serologic testing and the epidemiologic approach offers a solution of many of the difficulties encountered in getting patients under treatment. If they were generally applied the demand for treatment facilities would be from two to three times greater than at present

To the factors enumerated which operate to prevent persons infected with syphilis from seeking early and adequate medical care i.e. symptomless infection ignorance, carelessness, viciousness and the easy access to quack or drug store treatment, may be added one other factor which applies to early and late syphilis alike namely the ignorance of many physicians of the elementary methods of recognizing syphilis. Unfamiliarity with the dark field apparatus, a lack of understanding of the proper use or interpretation of serologic tests an absence of appreciation of syphilis as an infectious disease—these are the blinders which hamper the medical profession.

When syphilis is recognized and brought under treatment how effective is the profession in keeping it there for the required time? Again the question cannot be answered conclusively but reports submitted by approximately 3 000 clinics throughout the United States offer some clue as to the status of case-holding. From the first six months of 1939 through the first six months of 1940 the total number of admissions for syphilis to these clinics rose from a monthly average of 18,840 to 24,390 cases—an increase of approximately 30 per cent. However the average monthly patient-load in these same clinics over the same period of time increased from 210 000 to 368 000 cases—a rise of better than 70 per cent. This means

that the average duration of treatment for syphilis cases in the public clinics increased from approximately 11 months to approximately 12 months per case. Since the optimum average duration of treatment for early and late syphilis considered together is about two years, it may be estimated that present clinic facilities are perhaps no better than 50 per cent efficient in case-holding. While such detailed figures are not available for the private treatment of syphilis, it is doubtful whether case-holding by private physicians is more effective than that of the public clinics. Reduced to their simplest elements the factors that contribute to this poor showing are (1) the ignorance or carelessness of the treated patient, (2) the ignorance or carelessness of the treating physician, (3) the inconvenience and relative inaccessibility of treatment and (4) the expense of treatment.

The remedies for these several defects in our modern diagnostic and treatment set-up fall into three main categories: case finding, education and an expansion and alteration of existing treatment facilities.

The rôle of the medical profession in the control of syphilis — Trained medical personnel is essential. This comprises three categories of physicians: (a) venereal disease control officers, (b) clinic physicians, (c) private practitioners.

The first qualification for State and large municipal health departments, really desirous of controlling syphilis, is a full-time venereal disease control officer. This individual should combine in himself public health experience and wide clinical knowledge of syphilis, since he must deal not only with the public health problems raised by syphilis but also with its diagnosis and treatment. He must serve as consultant to clinic physicians and private practitioners alike. Until recently there were almost literally no physicians qualified in both these fields. Within the past several years, however, training centers for venereal disease control officers and other physicians have been established, with the collaboration and support of the United States Public Health Service, in several university centers in New York, the District of Columbia, Maryland, Tennessee, Ohio, Pennsylvania, Massachusetts and California. The training course at the Johns Hopkins University Schools of Hygiene and Medicine is designed primarily for present and future full-time venereal disease control officers. These training centers should be more widely utilized.

Health departments must of necessity operate venereal disease clinics and these clinics should be staffed by physicians who are well trained in the diagnosis and treatment of syphilis. At present the average health department clinic is usually under-manned and over-crowded, so that the under-paid doctor is literally unable to do anything else but give "shots," with little or no notion of what he is really accomplishing. Too often the patient is treated only on the basis of a positive serologic test, with no knowledge of the physician as to whether the syphilitic infection if really present is early or late, whether he is dealing with primary syphilis or paresis. Clinics must be better housed and better staffed. The staffs must be better paid in order to attract better men. The staffs must be better trained, both in diagnosis and treatment, both in technique and

practice Most health department clinics would be markedly improved if the health department would arrange special training periods at the medical centers now available for their own clinic personnel.

The private practitioner is responsible for many syphilitic patients The standards of diagnosis and treatment in private practice need to be measurably improved if the majority of private patients are to be handled even as well as in the poorest clinic practice The experience of Gehrmann of the du Pont Company constitutes an indictment of the management of syphilis in private practice which American medicine would do well to ponder The du Pont Company does routine serologic tests on all new employees. Those with positive tests are not treated by the Company but are referred to their private physicians Listen to Gehrmann's story of what happens

> Most physicians demand prices for treatment that are beyond the means of the individuals and out of reasonable proportion to their incomes. Some physicians maintain these high prices despite the fact that they are receiving arsphenamine, neo-arsphenamine and bismuth free of cost from their state.
>
> Many physicians refuse to treat the referred cases, stating that no treatment is indicated in spite of four plus Kahn and Wassermann reactions although the cases have never received adequate treatment.
>
> Numerous physicians refuse to admit that their patients have syphilis (again in the face of four plus Kahn and Wassermann reactions) This group denies the validity of blood tests and states that they have known their patients for years, and further know these same patients could not have contracted syphilis without their (the doctors') knowledge.
>
> On several occasions the attending physician has sent a blood specimen to a private or state laboratory and the report has come back that the reaction is negative. In every instance the results obtained by the company laboratory have been corroborated by subsequent check, but the attending physician has not always admitted that the patient has syphilis.
>
> Many cases are discharged as having had sufficient treatment, after three to ten injections of neo-arsphenamine without a heavy metal.
>
> Some have been reported as being well after a few mercury inunctions or a few intramuscular injections of water-soluble bismuth.
>
> Some are being treated with pills and nothing else.

For these private practitioners whose ideas of the modern treatment of syphilis are as Gehrmann's comments suggest, still "in the horse-and-buggy age" the training courses at the university centers named are also open and should by all means be utilized.

A syphilis control programme must have the cooperation of the entire medical profession.

It must be kept in mind that syphilis is the only major infection the spread of which in the community can be controlled alone by treatment of the infectious patient and by no other method. This fact makes it necessary for the public health authority to enter into the field of the treatment of disease in a manner unnecessary with any other infection It is this fact which is responsible for the growth of free clinics for the treatment of syphilis in large part sponsored by health departments. The establishment of such clinics on a comparatively small scale in the past and

on an ever-expanding scale at present has led to a feeling of resentment on the part of many private practitioners on the ground that the state is entering into competition with the practitioner is depriving the practitioner of income to which he is justly entitled and is providing the entering wedge for the appearance of state medicine.

The answers to these objections seem quite obvious The Federal Government through the United States Public Health Service has done no more than to summarize information concerning the prevalence, incidence and treatment of syphilis furnished by physicians themselves. The private practitioner has given ample evidence over the past 150 years that he cannot control syphilis single-handed. As a matter of fact, it is unfair to ask him to do so Since at least half of all the syphilitic patients to be treated can pay no part of the cost of their treatment and a large proportion of the remainder only a small part of its cost, it is only to be expected that the private practitioner will object to devoting so much of his own time and his own money to the tedious treatment of wholly or partly indigent people.

There is no danger that the setting up of adequate community facilities for syphilis control will start the medical profession on the path toward state medicine The private practitioner should welcome the relief which an adequate public syphilis control programme will give him. He need not fear the loss of patients. Anyone familiar with clinic practice in the treatment of syphilis knows that the syphilitic patient who can pay for all or part of his treatment will not submit to the overcrowding, long delays publicity routinization and lack of personal contact with his medical adviser which clinic treatment entails. The only patients who go to clinics are those who cannot afford to go anywhere else. What is needed in the syphilis control campaign is not curtailment of public facilities but sweeping additions to them in every state in the country

There should be provided in all State Health Departments a Division of Venereal Disease Control, which is primarily syphilis control. Divisions of venereal disease control should everywhere provide adequate epidemiologic service available not only to state and municipal health department clinics and to clinics operated by privately endowed charitable agencies, but to the private practitioner as well. Such divisions of venereal disease control should also provide follow-up service with the important aim of holding the infectious syphilitic patient to treatment beyond the point of *disappearance of symptoms of restoration of health and working capacity* and up to the point of disappearance of infectiousness. Such venereal disease control divisions must provide clinic service both free and part pay and must expand this clinic service to the point of care not only of all indigent syphilitic patients who apply but of all those who can be found by deliberate search. In most communities in the country this will involve a three- to four-fold expansion of existing facilities

The Expansion and Alteration of Existing Treatment Facilities

Facilities for the treatment of syphilis are provided by physicians in private practice who according to state reports for 1940 care for 40 per

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The trend of syphilis in the United States —For at least 5 years there has been reason to believe that fresh infections with syphilis in the United States were on the decline. The evidence on which this opinion was based was nevertheless scattered incomplete and in many respects unconvincing. Now however data are available from the examination of selectees of the United States Army which clearly show that a marked decline has actually occurred.

During World War I routine serologic tests of draftees were not performed but figures are at hand to show the incidence of *clinical* manifestations of syphilis in the second million drafted men In the operation of the present Draft Act, routine serologic tests are performed on all selectees and there are available for comparison not only the incidence of clinical manifestations of the disease but of latent syphilis as well. We quote from Parran Surgeon-General, U S Public Health Service (The Function of Public Health in Defense J.A M A. 117 186 [July 19] 1941) —

> Among the first million men [examined 1940–1941] 48 000 cases of syphilis have been found *Of these only 3 per cent showed clinical syphilis.* Among the second million draftees in the World War there was seven times this amount of clinical syphilis. In other words in 1917 clinical syphilis caused the rejection of approximately ten thousand men [per million] Now the number is one thousand four hundred and eighty two per million

Parenthetical words ours

CHAPTER XXXIII

THE INTENSIVE ARSENOTHERAPY OF EARLY SYPHILIS*

Background of the method —The original failure of the cure of early syphilis by a single injection of an average therapeutic dose of salvarsan led to many attempts at more intensive treatment by various expedients e.g., increasing the size of the dose increasing the frequency of injections of arsenic the combination of chemotherapy and fever therapy None of these was successful, because of the increased danger of the method employed, the high incidence of early or late relapse, or both.

In 1933 however Chargin and Leifer impressed by the earlier (1931) demonstration by Hyman Hirshfeld, and Wanger that large doses of many toxic substances could be administered parenterally to experimental animals provided the injections were given slowly over a long period of time by continuous intravenous drip began the treatment of early syphilis with large doses of neoarsphenamine (4 0–5 0 gm.) administered in divided doses in 5 percent glucose solution by intravenous drip 10 hours daily for a 5 day period. No other treatment was given. Twenty-five cases were treated and the immediate results were reported in 1935 Although these were encouraging, the work was unavoidably interrupted until 1938. An additional 86 patients were then treated with neoarsphenamine, this series being again interrupted by the death of a patient from toxic encephalopathy This death led to the substitution of mapharsen for neoarsphenamine and Chargin, Leifer and Hyman treated an additional 275 patients with this drug. The intravenous drip method and the five day duration of treatment were retained the total dose of mapharsen was gradually and tentatively increased from 400 mgm. in the first patients treated to a maximum of 1200 mgm.

Meanwhile, apparently independently and unaware of the American work Tzanck in France (1937) reported the administration of neoarsphenamine by intravenous drip (1.5 gm every other day for a total of 3 treatments) The method was discarded when the two hundred and twelfth patient died.

Meanwhile also the encouraging results reported in a series of papers by the Mount Sinai group led to the adoption of the intensive method or some modification of it by many North and South American workers, and something over 5000 patients have now been so treated.

Clinical modifications of the intravenous drip five day treatment —It is at once apparent of course that the originally proposed method is subject to modification in at least five respects (1) the substitution of multiple injections for intravenous drip thus (if successful) perhaps obviating the necessity for hospitalization (2) some alteration of the arbi

* A portion of this chapter dealing with experimental studies is taken verbatim from recent papers by Eagle and Hogan.

trarily chosen five day duration of treatment (3) more accurate delineation of the minimal and maximal effective dosage of arsenical drugs (4) the possible downward adjustment of arsenical dosage or the improvement of results by combining heavy metal and arsenical therapy and (5) the possible use of combined fever and chemotherapy Various workers have undertaken study of the first four of these points in man (Schoch and Alexander Shaffer Thomas Kaplan and others) still others have devoted their major effort to a study of the fifth (Thomas Warren and Carpenter Simpson and his Dayton associates) One investigator (Kaplan) has attempted to determine the applicability of the method to late syphilis

Clinical Results of Intensive Arsenotherapy in Early Syphilis

The published reports plus many others available through personal communication (see bibliography) deal almost entirely with one or another modification seeking to compress the treatment of early syphilis

TABLE 121

THE IMMEDIATE RESULTS (6 MONTHS TO 5 YEARS) OF THE INTENSIVE ARSENOTHERAPY OF EARLY SYPHILIS

Factor	Result
Patients completing treatment	95–98 percent
Disappearance time of surface treponemes	24 hours or less
Healing of lesions	5 to 15 days
Average time of serologic reversal	12–16 weeks
Prolonged serologic negativity (serologic "cure")	80–90 percent
Infectious relapse (including probable reinfection)	5–15 percent
Seroresistance (without clinical relapse)	5–10 percent
Asymptomatic neurosyphilis	1 percent or less
Observed late progression or relapse	None

within a period of 10 days or less. As nearly as can be determined, the results of treatment with comparable dosages are essentially similar whether the method employed is intravenous drip or multiple injections These results are summarized in Table 121 These *immediate* results are as good as and in some respects better than those obtainable with prolonged "standard (12–18 months) treatment (cf Chapter XIII) Several of the points enumerated in Table 121 require further comment

Patients completing treatment —It is apparent without argument that if a safe and successful method of treatment can be completed within a few days it is applicable to almost all patients with early syphilis, not only to their own benefit but also to that of the public health. In the intensive schemes requiring hospitalization (intravenous drip combined fever and chemotherapy) 95–98 percent of patients complete treatment early signs of arsenical intolerance cause suspension of it in only a few With intensive treatment on an ambulatory basis capable of completion within a few days or even a few weeks, many more patients can be held to completion than with the prolonged methods heretofore in vogue. Success-

fully to persuade patients to undergo the long grind of prolonged (12–18 months) treatment is in large part a function of the excellence of the follow-up service in the individual clinic. The best do no better than to complete such treatment in about 80 percent, the worst in only 20 percent or less. In this respect, intensive methods hold an incomparable advantage over prolonged methods.

The average time of serologic reversal.—Curiously enough, the rate of serologic reversal in early syphilis with intensive arsenotherapy by any scheme so far tried (average 12–16 weeks after completion of treatment) does not differ significantly from the observed rate under the older method of weekly injections of an arsenical drug. Unfortunately different statistical methods of computing the rapidity of quantitative fall in reagin titer do not lend themselves to exact graphic reproduction. In our own experience however and in that of others available to us through personal communication the rate of fall in quantitative reagin titer and the percentage probability of serologic reversal within a given time period are identical, regardless of the method of treatment, provided the total arsenical dosage is approximately the same. Curves of rate of reagin fall with intensive treatment seem to be directly superimposable (allowing for statistical error) on the curves of Figure 25 (p 215) or Figure 88 (p 528) of this book (based on weekly arsenical dosage.)

This fact suggests that the influence of arsenical treatment on serologic reversal in early syphilis is largely if not wholly a function of the effect of the first few injections of the drug, within limits regardless of the size of the dose and raises the probability of future information to be gained by experimental and clinical study

It should be unnecessary to re-emphasize here that the rate of serologic reversal with any particular serologic test is a function of the relative sensitivity of that test. In further studies of intensive arsenotherapy it is wholly unimportant to utilize a battery of several tests (except in so far as this may be valuable from the purely serologic standpoint of study of their relative sensitivity) Much more desirable is *serial quantitation* of a single test by whatever serologic technique is known to be reliable.

A word of caution is however essential. The statement has been made that in patients with early syphilis treated by combined fever and chemotherapy relapse has never been observed after the quantitative Kahn titer had reached zero. This implies some special virtue in the quantitative Kahn test not possessed by other serologic techniques. Similar claims have been made many times in the past, only to be upset by the mere passage of time or by the development of new and more sensitive serologic tests.

Prolonged serologic negativity.—The period of study of patients with early syphilis treated by one or another intensive method exceeds one year in only a few hundred, and five years in a very few indeed Nevertheless, three facts stand out clearly (1) when seronegativity is attained, it usually persists for so long as observation is as yet available (2) isolated serologic relapse, not accompanied or followed by evidence of infectious muco-cutaneous relapse, is rare and (3) most such relapses, combined

trarily chosen five day duration of treatment, (3) more accurate delineation of the minimal and maximal effective dosage of arsenical drugs (4) the possible downward adjustment of arsenical dosage or the improvement of results by combining heavy metal and arsenical therapy and (5) the possible use of combined fever and chemotherapy Various workers have undertaken study of the first four of these points in man (Schoch and Alexander Shaffer Thomas, Kaplan and others) still others have devoted their major effort to a study of the fifth (Thomas Warren and Carpenter Simpson and his Dayton associates) One investigator (Kaplan) has attempted to determine the applicability of the method to late syphilis

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However this may be the relapses so far recorded after the intensive arsenotherapy of early syphilis are practically all muco-cutaneous, chancriform monorecidives Ocular relapse and neurorecurrence do not seem to have occurred. The majority of relapses (or reinfections) are within 6 months of the completion of treatment and practically all within the first year

The practical implications of this fact are clear all patients treated by any intensive method must be carefully followed for a minimum period of one year with clinical and quantitative serologic reexamination at frequent (if possible, at monthly) intervals.

The recorded incidence (5–15 percent) of infectious relapse after intensive arsenotherapy is about the same as after 5–10 weeks of routine weekly arsenotherapy (cf pp 24–25)

The intensive re-treatment of infectious or serologic relapse — A number of patients have been subjected to intensive re-treatment following relapse infectious or serologic or after prolonged failure to attain serologic reversal (seroresistance) * It is difficult to determine accurately from the published data the results of re-treatment but in general they seem to be considerably less satisfactory than those of the original intensive course This is a not unexpected observation since under any system of treatment so far devised, a small proportion of patients with early syphilis seem fore-doomed to treatment resistance or to eventual relapse (cf p 226)

Asymptomatic neurosyphilis —The spinal fluid has been examined at some time after intensive treatment in more than 1000 patients though in most instances not repeatedly over a several year period The incidence of observed laboratory abnormalities is apparently well under 1 percent. This is to be compared with an incidence of abnormal fluids of 15–25 percent in patients with early syphilis treated by "standard" prolonged methods, the variation depending on the amount of treatment given before fluid study The advantage of intensive over prolonged methods of treatment in this respect appears overwhelming, especially if further observation of intensively treated patients reveals that originally normal fluids do not show evidence of relapse.

Observed late progression or relapse —There are no recorded examples of the development of benign late (gummatous) visceral cardiovascular or neurosyphilis after the intensive arsenotherapy of early syphilis. However the observation periods are very short, and the *ultimate* results in these terms will not be known for 25–30 years.

The Toxicity of Intensive Arsenotherapy

The successful adoption of a new method of treatment of disease depends not only on a demonstration of its therapeutic value, but on this

* The question as to when a patient with early syphilis intensively treated shall be regarded as seroresistant and eligible for re-treatment by an intensive or any other scheme is not yet settled but the available information to date indicates that in the absence of clinical relapse, such re-treatment should be postponed for at least 12 months after completion of the original course.

factor compared to the risk involved. A treatment which simultaneously cures the disease and kills the patient is to put it mildly undesirable. The intensive arsenotherapy of early syphilis as so far reported with treatment compressed into 10 days or less has carried with it an excessive risk.

It must not be forgotten that early syphilis is not *at the time* a serious disease. Few patients are even mildly ill from it practically none dies. If illness, incapacity or death does occur it is customarily delayed for 10 20 30 or even more years after infection Likewise to be kept in mind is the relatively favorable ultimate prognosis of the untreated infection—

TABLE 122

MORTALITY RATE OF INTENSIVE ARSENOTHERAPY OF SYPHILIS

(Including patients treated by any system of chemotherapy without added fever therapy and compressed into 10 days or less)

Cases treated	Drug employed	Method of treatment	Total dosage	Duration of treatment	Deaths	Toxic encephalopathy with recovery
about 4969 (compiled from literature and personal communications; references in bibliography)	Neoarsphenamine 793	I V drip or multiple injections	4–6 gm.	1–10 days	9 (one death in each 88 patients treated)	No definite statements available but at least 4
	Mapharsen about 3906		800–1600 mgm.		16 (one death in each 250 patients treated)	at least 27
	Neo or mapharsen (not separable from published paper) 270		as above		0	0

favorable, that is for the patient himself if not for the public health. Spontaneous "cure" is frequent about 65 per cent of untreated patients live so far as syphilis is concerned, happily ever after (cf pp 38–41) A treatment method which involves a substantial risk of immediate death for the sake of preventing potential but far from inevitable incapacity or death some decades hence is unjustifiable

The mortality rate of intensive arsenotherapy —Data have now accumulated on nearly 5000 patients treated by intensive chemotherapy (without combined fever therapy) within a 1–10 day period (Table 122) Among these are 25 recorded deaths i.e. one death in each 200 patients treated. Insofar as the literature permits these data have been further broken down into a comparison of the only two drugs as yet employed on a large scale, neoarsphenamine and mapharsen (Cannon has recently employed old arsphenamine—606—but his series is too small for comparison) All except 19 of the 793 neoarsphenamine-treated patients of Table 122 were given the drug by intravenous drip in a 3–6 day period. Of

the about 3906 mapharsen cases more than 1500 were treated in the same manner in the remainder some (exact number not available) received the drip method others multiple injections. The mortality rate from neoarsphenamine is 2.5 times greater than that from mapharsen and in the hands of most workers, neoarsphenamine has properly been abandoned

A comparison of mortality from intravenous drip and multiple injections is not exactly available, since certain authors (e.g. Elliott and his associates reporting 2000 intensively treated cases) do not specify the numbers treated by the two methods Nevertheless, the literature provides data on more than 2000 cases definitely known to have been treated by intravenous drip (Table 123) The greater toxicity of neoarsphenamine

TABLE 123

COMPARATIVE MORTALITY FROM INTENSIVE ARSENOTHERAPY BY INTRAVENOUS DRIP METHOD

(including only those cases in which method of treatment—without added fever therapy—is accurately defined)

Drug	Cases treated by I V drip	Deaths	Toxic encephalopathy with recovery
Neoarsphenamine	774	8 (one death in each 97 patients treated)	unknown but at least 3
Mapharsen	1534	8 (one death in each 191 patients treated)	not definite, but at least 17

is again evident but even with mapharsen, the death rate is about one in each 190 patients so treated.

The intravenous drip method accounts for 16 of the known 25 deaths. The mortality rate in those treated by multiple injection systems cannot be so accurately determined as yet but fairly definite estimates indicate that when treatment is compressed within 10 days or less the mortality is essentially the same, regardless of the method employed. This statement also holds true for combined fever and chemotherapy compressed within a 1–10 day period

A unilateral polemic has developed among certain ardent and vocal advocates of intensive arsenotherapy as to a comparison of these mortality data (and the incidence of toxic encephalopathies, presently to be described) with those from a prolonged weekly treatment system. The argument has fallen into the trap of comparing the risks of intensive therapy *utilizing mapharsen* with prolonged systems *using the arsphenamines*. This monograph devotes much space (cf Chapter VII) to a discussion of arsenical reactions and the mortality rate of antisyphilitic treatment, practically all of which is based on the arsphenamines *Mapharsen in clinical dosage is a far less toxic drug* In our own experience now covering 10

years no deaths have occurred from its use. Excepting those due to intensive arsenotherapy (at least 17 so far recorded cf Tables 122 and 123) there are only 6 reported deaths from mapharsen in the entire literature to date (Levin and Keddie) in spite of the enormous number of patients treated with it There has been only one death in the U S. Navy from more than one million doses of this drug If mapharsen is substituted for any arsphenamine product in such a prolonged weekly treatment system as is described in Chapter XIII the mortality rate may be expected to be essentially nil

Toxic encephalopathies from intensive arsenotherapy —The majority of the recorded deaths from intensive arsenotherapy have been from so-called hemorrhagic encephalitis (cf pp 111–113) now more appropriately named 'toxic encephalopathy This reaction exceedingly rare even with the arsphenamines before the advent of intensive arsenotherapy (one example in each 27 500 patients in the Johns Hopkins material) has occurred at least once in every 100 patients treated with 10 day or shorter intensive systems It has included mild mental confusion usually associated with severe headache and fever convulsive episodes one or many and coma. About half the patients recover the other half die Usually the reaction appears in the midst of treatment, when a total of 400–500 or more mgm of drug has been given but it may be postponed until 1–5 days after completion of treatment. It is associated with a striking excess of protein in the spinal fluid (Thomas Wexler and Dattner) and its onset may be predicted in certain patients by repeated spinal fluid examination during treatment If it occurs antisyphilitic treatment must of course be suspended and it is questionable whether arsenical therapy intensive or otherwise can be subsequently resumed with safety Treatment of the reaction itself is unsatisfactory adrenalin in large doses seems helpful (cf p 113)

The mechanism of development of arsenical toxic encephalopathy is unknown. By some workers in the intensive arsenotherapy field it is thought to depend on individual idiosyncrasy However its great frequency under these circumstances and its equally great rarity when arsenic is administered in smaller doses over longer time periods strongly suggests that it is dependent on the rapid administration of large doses

Necropsy studies of patients dying from toxic encephalopathy following intensive arsenotherapy have shown in some cases the typical pathologic picture briefly described on p 113 In others no structural alteration in the nervous system or elsewhere.

Other major reactions due to intensive arsenotherapy —These include toxic hepatitis blood dyscrasias renal disturbances dermatitis exfoliativa, and peripheral neuritis

The incidence of all of these except peripheral neuritis is apparently lower than with prolonged methods of treatment (possibly excepting renal complications from which at least 4 deaths are reported after intensive arsenotherapy) Their clinical manifestations and management do not differ from the descriptions of Chapter VII

Peripheral neuritis on the contrary which occurs with great rarity with

prolonged treatment systems (cf p 111) occurs in about 35 percent of patients given intensive treatment with neoarsphenamine and in 1–2 per cent of those so treated with mapharsen In the neoarsphenamine series it was often severe and temporarily crippling in the mapharsen series, it is usually mild and transitory consisting only of paraesthesias in the extremities without weakness or disability

Minor reactions of intensive arsenotherapy —These include so-called primary" fever (the Herxheimer effect, cf p 91) secondary' fever appearing 3–9 days after the start of treatment and usually though not always associated with erythematous toxicodermas (erythema of the ninth day cf p 101) headache gastrointestinal distress transitory albuminuria and transitory jaundice None is serious and none interferes with completion of treatment.

The experimental study of intensive arsenotherapy —The question which has been raised by the proponents of intensive treatment transcends the merits of the arbitrary 18 month schedule and the equally arbitrary intensive procedures which have been suggested to date *it is the more general question as to the optimum method for the treatment of early syphilis.*

In the evaluation of a new drug or of a new therapeutic procedure it is customary to determine toxicity and therapeutic efficacy in the experimental animal prior to clinical trial Unfortunately such experimental data were not at the outset available for any of these intensive schedules. In consequence the frequency of injection the total duration of treatment the size of the individual dose and the total amount of mapharsen administered had to be set empirically with no prior information as to the margin of safety thereby afforded

The rational approach to the problem involves the accumulation of basic experimental data as to how the therapeutic efficacy and toxicity of mapharsen are affected by varying the duration of treatment and the frequency of injections Without those data, any schedule, whether a five day intravenous drip daily injections for 20 days or weekly injections for 18 months is arbitrary and can be revised only empirically with no prior information as to the margin of safety afforded by the particular schedule used. With those data, it may be possible to effect schedules of treatment which represent a reasonable compromise between the excessively toxic five day procedure and the vexatious 18 month schedule in current use. Such a compromise might combine the speed of one and the safety of the other to an optimum degree while retaining the therapeutic efficacy of both.

The Mount Sinai workers and those who have been associated with them or have followed their lead have therefore rendered a signal service in reopening for consideration the entire question as to the optimum time-dose relationship for the treatment of early syphilis. For once the question is raised and we examine our standard practice critically without regard to the facts that it works or that it has been sanctified by long usage we find that (a) weekly injections are arbitrary (b) there is no good experimental evidence to indicate that alternation of arsenical and heavy metal

courses is necessary (c) the relative contribution of arsenical and of bismuth are unknown and (d) current practice of administering a standard dose usually with scant regard to large differences in body weight and

TABLE 124

THE THERAPEUTIC EFFICACY OF MAPHARSEN IN RABBITS IN RELATION TO THE METHOD AND DURATION OF TREATMENT

(after Eagle and Hogan)

Frequency of injections	Total duration of treatment	Total number of injections	Dose which cures 50% of animals (CD_{50}) mg./kg.	Minimal curative dose (>95% of animals "cured") mg./kg.
Weekly	6 weeks	6	4 0	8 5
Triweekly	4 weeks	12		
Daily	1 day 4 days 12 days	1 4 12	3 0	6 3
Multiple daily	1 day 2 days 4 days	4 4 16	2 4 2 7 1 5	5 9 6 5 3 6
Intravenous drip	1 day 2 days 4 days	— — —	5 2 3 8 4 34	9 8 6 8 11 2

with an arbitrary differentiation between the sexes is pharmacologically unsound.*

The toxicity therapeutic efficiency and chemotherapeutic index of intensive mapharsen therapy in experimental animals — The fundamental experimental data which must precede a natural clinical approach to the problem of intensifying the treatment of syphilis have

* The custom of variation in dosage of arsenical drugs for sex (e g., for a man, arsphenamine 0.6 gm neoarsphenamine 0.9 gm., mapharsen 0 060 gm.; for a woman, 0.4 0 6, and 0 040 gms. respectively) constitutes a three decade perpetuation of Ehrlich s original advice now known to be pharmacologically unsound but nevertheless still adhered to in most texts (including the earlier chapters of this one) and in the instructions of pharmaceutical manufacturers. There is no good evidence to indicate that kilo for kilo of body weight, the female differs from the male in ability to tolerate or utilize drugs, except in so far as an excessive amount of body fat (which may not participate in drug distribution or metabolism) may be concerned.

Intensive arsenotherapy has also prompted a re-evaluation of relation of drug dosage to body weight It is entirely illogical to assume that, e g 1200 mgm. of mapharsen administered in 5 days to a 220 pound (100 kg) man will have the same toxic and therapeutic effects as when given to a patient of either sex weighing half as much (110 lbs —50 kg.) Adjustment of dosage to body weight should in the future, therefore form an obligatory feature of any intensive treatment scheme adopted.

become available through the recent work of Eagle and Hogan. Their findings are summarized in Tables 124 and 125 and Figures 98 99 and 100 and merit careful scrutiny

1) On every schedule of injections tested whether weekly thrice weekly daily multiple daily or intravenous drip the total amount of mapharsen tolerated by rabbits could be increased apparently without limit, by prolonging the duration of treatment (Figure 98) Within a fixed

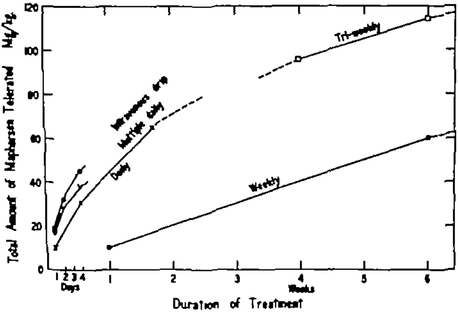


FIG. 98—The Maximum Tolerated Dose of Mapharsen in Rabbits in Relation to the Frequency and Duration of Treatment (after Eagle and Hogan)

time period more arsenical could be administered by increasing the frequency of injections but this factor was of altogether secondary importance as compared with the duration of treatment. Stated in reverse the toxicity of a given *total* dose of mapharsen increased in direct proportion as the *total time of its administration is decreased*

2) In complete contrast the *curative* dose of mapharsen was largely independent of the time and method of administration (Table 124) although the intravenous drip was consistently less effective than multiple injections over the same period of time Moreover comparing the various schedules involving acute injections, there was some indication that the more intensive the schedule of injections, the less arsenic was required to effect cure However these were relatively small differences, and some are certainly within the experimental error In the main, within the time limits of an intensive method, the curative dose of mapharsen in rabbits was largely unaffected by the method of administration.

3) From the clinical point of view neither toxicity nor therapeutic activity is the important factor but rather the ratio between the two giving the margin of safety (chemotherapeutic index) That margin of safety in rabbits is summarised in Figure 99 There is no optimum method for the treatment of syphilis On any schedule of injections whether weekly daily or four times a day one can obtain any desired margin of safety

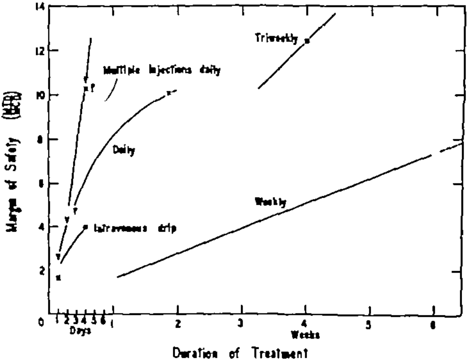


FIG 99 —The margin of safety of antisyphilitic treatment in rabbits in relation to the duration of treatment and the frequency of injections (after Eagle and Hogan)

by proper adjustment of the treatment period This follows directly from the fact that the tolerated dose increases with the prolongation of treatment while the curative dose is largely unaffected and is apparent from the curves in Figure 99

To a limited degree the treatment of syphilis can be intensified without sacrificing safety by giving a larger number of injections over a shorter period of time This is illustrated by the examples just cited, or in more general terms by the data of Figure 99 and in particular by Figure 100 The duration of treatment in rabbits may be shortened by approximately 50 to 65 percent without decreasing the margin of safety by giving mapharsen injection three times weekly instead of weekly and an even more

pronounced concentration may be effected by giving injections daily or several times daily

Contrary to what has been claimed for it in man, the intravenous drip

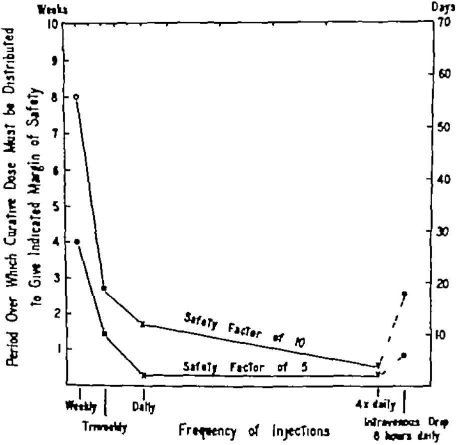


FIG. 100.—The degree to which antisyphilitic treatment in rabbits can be concentrated without affecting the margin of safety (after Eagle and Hogan)

Thus, for an arbitrary safety factor of 10 (upper curve), the total curative dose if given weekly must be distributed over 8 weeks, if given triweekly it may be concentrated to approximately 3 weeks daily injections retain the same safety margin if distributed over 12 days injections repeated four times daily permit the condensation of treatment to a 4 day period while the *intravenous drip, primarily* because of its lower therapeutic efficacy in rabbits must be continued for an approximate period of several weeks.

The lower curve relates the frequency of injections and the time necessary for their administration to attain an arbitrarily chosen margin of safety of 5, i e half as great as the upper curve

in rabbits does not permit the maximal safe condensation of treatment and is less effective in this respect than daily injections Indeed as is shown in Figure 100 for a comparable margin of safety it permits a con

densation of treatment only slightly greater than that effected by a triweekly schedule. This is due primarily to the low therapeutic efficacy of the intravenous drip

Any significant condensation of treatment beyond that permitted by daily triweekly or multiple daily injections can be effected only by decreasing the margin of safety As shown by any curve in Figure 99 one may arbitrarily give the curative dose of mapharsen in four weekly injections instead of ten, or in five daily injections instead of twenty but the necessary consequence of every such condensation is a decreased margin of safety and presumably an increased danger of toxic reactions

The relationship of toxicity and therapeutic efficacy to blood and tissue concentration of arsenic —In Chapter XXXIII of the first printing of the second edition of this monograph, and in publications by other workers on intensive arsenotherapy it was suggested that the efficacy of intensive treatment might depend on the maintenance of a critical treponemicidal level of arsenic in blood and tissues over a relatively prolonged period of time Unpublished data (Hogan and Eagle) indicate that a large and variable proportion of circulating blood arsenic is actually in the red blood cells rather than in the plasma. Further there is some reason to believe that the large proportion of arsenic eventually bound by and destructive to the treponeme is so bound within a short time after injection of the drug The excessively minute amounts demonstrable in the circulating plasma, even so soon as 30 minutes after injection can have but little treponemicidal action. Until there is more convincing experimental evidence, attempted analogies between arsenical and sulfonamide blood and tissue levels are wholly misleading

The applicability of experimental data to man —There is reason to believe that the same considerations observed in animals apply directly to man. In man as in rabbits the satisfactorily curative dose of mapharsen (arbitrarily taking as that amount for man the dose which renders more than 85 percent of the patients with early syphilis permanently seronegative and which it is hoped will prevent the appearance of late complications) seems to be largely independent of the method of administration and to be about 20 to 30 mg per kg or a total of between 1000 and 2100 mgs. for a 50–70 kg man. This is three to four times more than is required to cure a rabbit but is nevertheless a constant Attempts to use less mapharsen have given unsatisfactory results whether on intravenous drip or on multiple injections Moreover there seems to be no reason to doubt that the relative and perhaps also the absolute toxicity of the various procedures as determined in rabbits holds also in man Making that assumption and with the reservations thereby entailed tentative treatment schedules for man are summarized in Table 125 which illustrate the fact that the fixed curative dose of approximately 1500 mgs for a 60 kilogram weight can be administered with any desired margin of safety or any desired schedule of injections by suitable adjustment of the time period *In man, as in rabbits there is no optimum method for the treatment of early syphilis* An infinite number of permutations of time dosage and frequency are possible each with a calculable margin of safety and a correspondingly predictable incidence of serious toxic reactions.

Just what does represent an adequate margin of safety an allowable incidence of serious reactions and an allowable mortality is an open question A nice balance must be struck between safety speed and convenience. In Table 126 are listed the intensive procedures which have been used in man and the margin of safety for each as calculated from the experimental data of Eagle and Hogan. The correlation between the calcu-

TABLE 125

ESTIMATED MARGIN OF SAFETY IN MAN AFFORDED BY VARIOUS TREATMENT SCHEDULES

"Curative Dose" taken as 25 mg./kg., or a total of 1500 mg. in man weighing 60 kg Maximal Tolerated Dose on various schedules extrapolated from rabbit data.

(after Eagle and Hogan)

Frequency of Injections	MARGIN OF SAFETY 2	4	6	8	10
	ESTIMATED AMOUNT OF TREATMENT WHICH WILL GIVE INDICATED MARGIN* (Duration, number of injections and individual dose)				
Weekly	8 weeks (8×200 mg.)	10 weeks (10×150 mg.)	15 weeks (15×100 mg.)	20 weeks (20×75 mg.)	25 weeks (25×60 mg.)
Tri-weekly	2 weeks (6×250 mg.)	4 weeks (12×130 mg.)	7 weeks (20×70 mg.)	12 weeks (36×40 mg.)	15 weeks (45×33 mg.)
Daily	8 days (8×180 mg.)	3 weeks (18×80 mg.)	6 weeks (36×40 mg.)	10 weeks (60×25 mg.)	
Four times daily	5 days (20×75 mg.)	15 days (60×25 mg.)			
Intravenous drip	5 days (5×300 mg.)	12 days (12×125 mg.)			
Estimated mortality	1:200	1:400	1:800	1:2000	<1:3000

* In man weighing 60 kg dosages would have to be revised up or down in accordance with body weight

lated margin of safety and the observed incidence of toxic reactions and death is to be particularly noted. It seems clear from that Table and from Table 125 that the high proportion of serious reactions and the high mortality of the five day intravenous drip or of any treatment procedure in which the curative dose of mapharsen is administered in ten days or less are both excessive and unnecessary Intensive treatment procedures can probably be devised in which the total duration of treatment is compressed to a reasonable 6 8 or 12 week schedule and in which the incidence of serious toxic reactions does not unduly exceed that of current clinic practice Dozens of schedules can be arranged, tailored to fit the needs of a particular clinic of a particular group of patients, or indeed the convenience of the individual physician or patient. Properly planned however with due reference to the basic experimental data, the intensive treatment of early syphilis, whether in 20 40 60 or 80 days, may be a feasible relatively safe and probably effective procedure and one which may

be expected to replace the 18 month schedule Several such schedules are now in use (cf Eagle and Hogan) and although it is too early to appraise their therapeutic efficacy the initial results with respect to both toxicity and efficacy are promising

One final point should be mentioned *The foregoing discussion is based almost in its entirety on laboratory and clinical experience with mapharsen*

TABLE 126

ESTIMATED MARGIN OF SAFETY AFFORDED BY SOME METHODS OF TREATMENT WHICH HAVE BEEN USED IN MAN

Method of administration	Mapharsen per dose[1]	Total duration	Amount of injections	Total dose of mapharsen in mg.	Estimated margin of safety	Estimated mortality
Intravenous drip	240	5 days	5	1200	2 5	1 200
Twice daily injections	60	10 days	20	1200	3	1 300
Daily injections	60	3 weeks	20	1200	5	1 400
Triweekly injections	60	6 weeks 8 weeks 10 weeks	18 24 30	1080 1440 1800	5– 7	1 400–1 1000
Twice weekly injections	*60*	*10 weeks* 20 weeks[2]	*20* 40	*1200* 2400	*7– 8*	*1 1000 1 3000*
Weekly injections	60	40 weeks	40	2400	9–10	less than 1 3000

In man weighing 60 kg. In some of these schedules, no attempt was made to adjust the mount of treatment for varying body weight in others the dose has been adjusted to approximately 1 mg./kg

In man weighing 60 kg.

Except for the omission of bismuth, this is essentially the method of treating syphilis recently adopted by the Army

any conclusions reached with respect to the optimum combination of time and dosage apply only to that drug and must be revised perhaps drastically if new compounds are developed deserving of clinical trial

Experimental studies of combined arsenic and bismuth therapy — Although the mechanism of action of bismuth in syphilis is not as clearly understood as that of arsenic (in itself not yet absolutely defined) there are some experimental data from Clausen Longley and Tatum to show that when arsenic and bismuth are administered concurrently to syphilitic animals the therapeutic efficiency of the drugs is additive while their respective toxicities remain unaltered. Whether as suggested above this observation is applicable to the intensive arsenotherapy of

early syphilis in man either in the sense of improving the results of the arsenical dosage remains the same (at a total of 20–30 mg/kg of mapharsen), or of obtaining equally satisfactory results as those currently achieved if mapharsen dosage is lowered, requires much further study Clinically this is in progress by parallel series of patients treated by 8–12 weeks' intensive schedules, with and without added bismuth

Experimental studies of combined fever and chemotherapy — An evaluation of the so-called 'one-day' treatment of early syphilis by simultaneous fever and chemotherapy now currently under study by the Dayton and Rochester groups requires much more accurate experimental data than those heretofore available It has long been known that both toxicity and therapeutic efficiency of many drugs are greater if administered to animals or man at fever temperatures than at normal body temperature There are no published data as to whether this is true in vivo (although the in vitro studies of Eagle indicate that arsenicals are more actively treponemicidal at higher temperatures) or if so whether toxicity and therapeutic efficiency increase in parallel thus retaining the same chemotherapeutic index at fever as at normal temperatures or whether the increase in one factor is greater than in the other and if so in which

In spite of this lack of fundamental knowledge efforts have been made to combine fever and chemotherapy in the treatment of early and late syphilis for more than 20 years (cf pp 233 and 399) None of these has been convincing and none has attempted to define the variables of height of fever drug dosage and duration of treatment Recently stimulated by the awakened interest in rapid methods of treatment, Hoak Warren and Carpenter have tentatively determined that (a) the toxicity of mapharsen for rabbits is approximately doubled when the drug is given to animals whose body temperature has first been raised to 41.5°C and maintained at this level for three hours and (b) its therapeutic efficiency under these same conditions is increased, perhaps as much as four-fold Further studies should permit translation of these data to man will save time in solution of the problem by avoiding prolonged empirical trial and will add greatly to the factor of safety in patients so treated

The Intensive Arsenotherapy of Syphilis in Pregnant Women

At least two studies (Sadusk and Shaffer Rattner) are in progress on the effect of intensive arsenotherapy administered to pregnant syphilitic women in the prevention of congenital syphilis in the fetus [illegible] a small number of mothers has been treated, and the results as to the effect [illegible] are not as yet convincing The known higher incidence of the [illegible] reactions of acute yellow atrophy and toxic encephalopathy in pregnant as compared with non-pregnant women or men (cf p 450) indicates the need for caution and much further information before the general applicability of intensive therapy during pregnancy can be determined Thus far serious reactions have not occurred in the small series so treated

The Intensive Arsenotherapy of Late Syphilis

Several questions have not been considered in the present discussion which are none-the-less of primary importance One is the applicability of

an intensive procedure to clinical conditions other than early infectious syphilis Kaplan has reported his experiences with the intravenous drip in in the treatment of latent syphilis asymptomatic neurosyphilis and late syphilis. The evaluation of therapeutic efficacy in latent and late syphilis is however even more difficult than in the case of early syphilis The serologic response in such patients is usually minimal on any plan of treat ment and is moreover of little or no prognostic significance Even without treatment a large proportion of patients with latent syphilis develop no demonstrable late complications and so long a period is required to deter mine the presence or absence of clinical signs of progression or relapse that the proper evaluation of therapeutic efficacy will require perhaps 20 to 30 years of observation in a relatively large group of patients.

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CHAPTER XXXIV

VENEREAL DISEASE CONTROL IN THE ARMY AND NAVY*

THE CURRENT (*1942*) *venereal disease incidence rates in United States Army and Navy are each about 40 per 1000 strength per annum. The announced strength to be reached by the Army in 1943 is 7,500 000 men by the Navy 1,500 000 If the present venereal disease incidence rates are not significantly lowered there will be among 9 000 000 men in the Armed Forces 360 000 fresh infections per year accounting for at least 7,200 000 lost man days This is equivalent to loss from the guns of the entire time of 20 000 men for one year and puts out of action the equivalent personnel of two armored divisions or ten aircraft carriers!*

* * *

The venereal diseases in the United States Army and Navy are still as they always have been a problem of the first magnitude Except in the event of epidemics of other acute infectious diseases they remain as they always have remained the major infectious disease problem which the Services face. Their importance is increased as always under war conditions

The high incidence of venereal diseases is of military importance because of loss of manpower and overburdening of available hospital facilities of civilian public health importance because of their additional spread to the civilian community by infected military and naval personnel, both during and after their period of service of individual importance because of the disability they produce and of importance to the taxpayer because of the cost of treatment of infected personnel and of compensation for subsequent disability

Venereal Disease Incidence in the Armed Forces in Peace and War

The data as to venereal disease incidence in the United States Army cover four wars During the first three of these the Mexican, Civil and Spanish Wars and in the years between them no special measures for venereal disease control were undertaken In each of them the annual incidence rate per thousand strength approximately doubled to fall back after demobilization to an average of about 80 per thousand annually After the Spanish-American War the peace time drop was delayed about ten years and was to a somewhat higher level about 90 to 100 per thousand

World War I —In World War I on the contrary specially trained venereal disease control officers were called into the Army in large numbers In the American Expeditionary Force in France, no less than 246 officers were assigned to this duty a rough proportion of one military venereal disease control officer to each 10 000 troop strength.

* Dr Frank W Reynolds has ably assisted in the preparation of this Chapter

This concentration of venereal disease control effort was productive of a result not attained in any previous war The incidence rate rose briefly from its average prewar level of 90 to about 110 per thousand but thereafter and actually during the course of the war it fell to about 60 Instead of doubling under wartime conditions as always previously it nearly halved In the Navy too the incidence rate fell during the three years of World War I from its previous ten year average of 90

Even this spectacular result was however a relative achievement only During the thirty-three month period of World War I April 1 1917 to

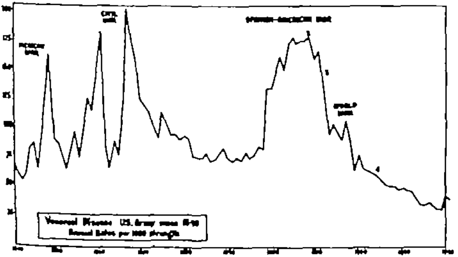


FIG. 101

December 31 1919 there were reported in the United States Army 483 717 and in the Navy 57 146 cases of freshly acquired or freshly discovered venereal disease. These accounted in the two Services for 7 492 610 lost man-days the equivalent of the absence from duty of 21 000 men for one full year and for more casualties than from wounds in battle.

The interim period —After World War I with the demobilization of the military and naval forces there was a concurrent and complete demobilization of the corps of trained venereal disease control officers, and a drastic reduction of funds from the Federal Government for the control of venereal disease in the civilian population. Venereal disease in the Army and Navy reverted to its customary status in time of peace in which it was the job of every medical officer and hence the responsibility of no one in particular Nevertheless rates in both Army and Navy continued to fall.

From the data of Figure 102 it appears that the incidence of syphilis has declined at a more rapid rate than that of other venereal diseases The syphilis incidence rate is now lower than at any time in the history of the Services. The proportion of syphilis to other venereal diseases which two decades ago was about 1 5 is now about 1 9 This fall in syphilis incidence parallels a similar fall (to 1940) in the civilian population.

U. S. ARMY		
Year	Total Venereal Disease	Syphilis
1920	78 03	13 92
1921	62 66	10 74
1922	63 07	13 33
1923	56 95	13 76
1924	57 15	13 80
1925	53 75	11 10
1926	54 59	12 18
1927	54 78	11 56
1928	49 91	10 89
1929	51 47	12 69
1930	52 53	12 58
1931	49 80	13 41
1932	46 48	14 26
1933	37 63	11 58
1934	38 21	9 22
1935	35 99	8 40
1936	36 96	8 03
1937	34 2	8 16
1938	32 67	9 12
1939	30 94	7 12
1940	41 85	7 29
1941	40 50	5 70



U. S. NAVY		
Year	Total Venereal Disease	Syphilis
1920	126 18	17 54
1921	120 05	17 84
1922	127 36	20 03
1923	123 33	18 63
1924	137 57	19 74
1925	126 56	19 60
1926	118 82	23 02
1927	132 27	24 57
1928	124 11	22 69
1929	127 51	21 64
1930	133 91	25 03
1931	136 79	25 46
1932	133 62	27 66
1933	102 45	24 39
1934	90 28	20 59
1935	74 70	14 07
1936	65 49	11 07
1937	63 90	11 08
1938	77 45	12 59
1939	85 87	12 90
1940	80 27	8 90
1941	50 24	5 65

FIG. 102.—Venereal Disease and Syphilis Incidence Rates in U. S. Army and Navy 1920–1941

SYPHILIS CONTROL ACTIVITIES REPORTED FOR STATES AND TERRITORIES

UNDER PROVISIONS OF THE VENEREAL DISEASE CONTROL ACT

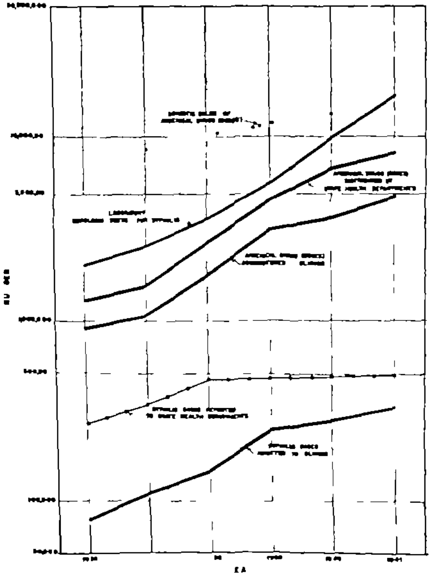


FIG 102

Figure 102 also emphasizes the fact that the Navy rate has been consistently higher than that of the Army and indicates that the control of venereal disease in our sailors is a challenging public health problem indeed

The current incidence in Army and Navy —Current rates have

fallen, both in Army (in 1939 since when there has been a significant rise) and Navy (in 1941) to the lowest levels in their respective histories There is reason to believe however that these rates are relative rather than absolute and are materially lower than actual rates In the continental United States if not abroad concealment of disease self treatment treatment by civilian physicians are all practiced to an unknown extent, largely because of retention by the Services of punitive measures (see below) There is likewise reason to believe that the fall in Service rates far from being a matter for Service self-congratulation is a reflection of lowered venereal disease incidence in the civil population

As to syphilis if not to other venereal diseases there is convincing evidence that the nation wide control effort sponsored by the United States Public Health Service under the leadership of Parran and Vonderlehr had begun to produce results up to the outbreak of this war Some of the achievements of this effort are graphically presented in Figure 103 The best proof however lies in the examination of selectees in this war as compared with World War I

In 1917–1919 routine serologic tests were not employed in the examination of selectees. In the second million drafted men of that War 15 per 1000 examined had obvious and clinically apparent syphilis.

In this war routine serologic tests have been employed in all soldiers and sailors entering the Services whether volunteer or under Selective Service. The prevalence of syphilis thus discovered in the first million men examined under Selective Service is 45.2 per 1000 but the incidence of *clinically apparent syphilis* is only 1 4 per 1000

The distribution of syphilis among selectees serves as an index of its prevalence in the civilian population as a whole These data, mapped in Figure 104 show the trouble spots to be Southern and Southwestern States precisely those in which the largest troop training concentrations are located The interrelationship of military and civilian venereal disease incidence is demonstrated by comparing the map of Figure 104 with those of Figure 105 Here are shown the 1941 incidence of syphilis for the nine Army Service Commands (formerly Corps Areas) and for the 16 Naval Districts In the Army the rates for the 8th, 4th and 7th (which includes Arkansas) Service Commands all located in the South and Southwest, are significantly high In the Navy the highest rates are in personnel *outside* the continental United States (the West Indies Philippines and Canal Zone) in this country 5th, 7th and 8th Naval Districts (all in the South or Southwest) join the 3rd (New York) in the unenviable distinction of the highest syphilis rates

Parenthetically the excessively high Navy rates in the West Indies, Philippines and Canal Zone are an indication that the major venereal disease problem in both Services is likely to be with personnel abroad rather than at home and strongly urges redoubled efforts at venereal disease control with troops on foreign stations

The Control of Venereal Disease in Civilian Life and Its Relation to the Armed Forces

The greatest single factor accounting for the decline of venereal disease in the civil population is the control organization built up through the United States Public Health Service in cooperation with State and local Health Departments. Since 1918 the Public Health Service has had a separate Division of Venereal Diseases, to which on June 5 1942 were attached 75 medical officers Each of the forty-eight States and the District of Columbia has created (most of them within the past five years) within the State Health Department a Division or subdivision of Venereal Disease Control and this example has been followed by practically every municipality in the country of 500 000 population or over

It was early recognized that the public health approach to venereal disease control required a group of physicians well grounded in the clinical aspects of these diseases and at the same time conversant with public health administration and the principles of epidemiologic procedure. It was necessary to create such a group of specially trained physicians from the ground up a task which is still proceeding Exact data as to the number of persons devoting full time to venereal disease control in the civil population are not available but a fair estimate is that at least one hundred State and local Health Departments possess such divisions

In their creation and development, special public health technics have been worked out, now so elaborate as to justify monographic presentation (by Nelson and others) We have gone far in our armament against syphilis since World War I Serologic tests have been perfected and standardized, laboratories have been multiplied and improved arsenicals are more freely and conveniently available, and facilities for treatment at nominal cost have increased more than 100-fold since 1917 (see Figure 103)

The civil public health authority has learned its lesson that as long as venereal disease control is the job of every public health officer and of every civilian physician, it is the job of nobody and results are invisible.

The Armed Forces of course, recognize the relationship between civilian and military venereal disease rates Military and naval personnel acquire these infections obviously from the civilian population and the Army and Navy are therefore thoroughly justified in insistence on heightened effort at venereal disease control among civilians But soldiers and sailors also *spread these diseases to civilians and the proximity of large* concentrations of service personnel multiplies both the work and the responsibilities of the civilian agencies. Only by interlocking responsibility and close cooperation can proper control procedures be effected.

Soon after President Roosevelt declared the first "limited emergency" in 1939 the War and Navy Departments, the Federal Security Agency and the various State Health Departments drew up an eight point Agreement on measures for the control of venereal diseases in areas where Armed Forces or national defense employees are concentrated. This Agreement, which forms the backbone of the war time venereal disease control program is reproduced as Figure 106

An Agreement by the War and Navy Departments, the Federal Security Agency and State Health Departments on Measures for the Control of the Venereal Diseases in Areas Where Armed Forces or National Defense Employees are Concentrated[1]

It is recognized that the following services should be developed by State and local health and police authorities in cooperation with the Medical Corps of the United States Army the Bureau of Medicine and Surgery of the United States Navy the United States Public Health Service, and interested voluntary organizations:

1. Early diagnosis and adequate treatment by the Army and the Navy of enlisted personnel infected with the venereal diseases.

2. Early diagnosis and treatment of the civilian population by the local health department.

3. When authentic information can be obtained as to the probable source of venereal disease infection of military or naval personnel, the facts will be reported by medical officers of the Army or Navy to the State or local health authorities as may be required. If additional authentic information is available as to extramarital contacts with diseased military or naval personnel during the communicable stage,[2] this should also be reported.

4. All contacts of enlisted men with infected civilians to be reported to the medical officers in charge of the Army and Navy by the local or State health authorities.

5. Recalcitrant infected persons with communicable syphilis or gonorrhea to be forcibly isolated during the period of communicability; in civilian populations, it is the duty of the local health authorities to obtain the assistance of the local police authorities in enforcing such isolation.

6. Decrease as far as possible the opportunities for contacts with infected persons. The local police department is responsible for the repression of commercialized and clandestine prostitution. The local health departments, the State Health Department, the Public Health Service, the Army and the Navy will cooperate with the local police authorities in repressing prostitution.

7. An aggressive program of education both among enlisted personnel and the civilian population regarding the dangers of the venereal diseases, the methods for preventing these infections, and the steps which should be taken if a person suspects that he is infected.

8. The local police and health authorities, the State Department of Health, the Public Health Service, the Army and the Navy desire the assistance of representatives of the American Social Hygiene Association or affiliated social hygiene societies or other voluntary welfare organizations or groups in developing and stimulating public support for the above measures.

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[1] Adopted by the Conference of State and Territorial Health Officers, May 7-12, 1940.

[2] Familial contacts with naval patients will not be reported.

Venereal Disease Information September 1940

U. S. ARMY: M.C. [illegible] U. S. NAVY: [illegible] (071) (7-30-40)

U. S. Public Health (9-5-40) [illegible]

Federal Security Agency

VD-1177 United States Public Health Service

Fig. 106

The several points dealt with in this Agreement may be briefly amplified as follows

Early diagnosis and treatment by the armed forces —No other large organizations provide more adequate facilities for diagnosis and treatment of the venereal diseases than do the United States Army and Navy Long cognizant of the importance of their problem the Medical Corps of the respective Services have made facilities for diagnosis and treatment freely and conveniently available and have supplemented these with educational programs and case-finding methods inapplicable to civilian practice.

Complete physical examination including a serologic test for syphilis, assures the Services that the recruit, volunteer or selectee, is free from venereal disease at the time of his enlistment or if infected, is promptly recognized as such and brought under treatment if necessary * Periodic physical inspections contribute to a relatively high discovery rate. Laboratory facilities for darkfield and serologic examinations are available under all except actual combat conditions.

The majority of cases of syphilis occurring in the Armed Forces are discovered in the early stages for which treatment schedules have been well standardized.** The average soldier sailor or marine receives treatment better than he would receive in civilian life.

However consultants specially trained in the clinical aspects of syphilis and other venereal diseases should be available at all large Army and Navy concentrations. It is an anachronism that in organizations where venereal infections contribute so largely to the number of lost man-days the diagnosis and treatment of these cases should be largely a function of the surgical urologist rather than of medical officers whose special interest is in venereal disease *per se* The present trend toward the creation of departments of Dermatology and Syphilology in Service hospitals is a step in the right direction.

The question of hospitalization —Modern chemotherapy being as effective as it is, both for syphilis and for other venereal diseases, it is evident that the ideal of adequate treatment does not imply prolonged hospitalization although this has been a more or less standard procedure in both Army and Navy The period of hospital confinement varies at the discretion of the medical officer but is rarely less than ten days and may exceed several months. The number of lost man-days is appalling (Figure 107) Navy procedure is clearly in advance of that of the Army the average Navy period of hospitalization being only 10–15 instead of the Army's 35–45 days.

Prolonged hospitalization, or indeed hospitalization of any duration, is

* Under the latest (March 15, 1942) provisions of Mobilization Regulations (MR 1–9), selectees with uncomplicated acute or chronic gonorrhea are eligible for immediate military service. It has been announced that soon (probably by January 1 1943), selectees with early or latent syphilis will also be accepted.

** The Army has just adopted a modified intensified treatment scheme applicable alike to early and latent syphilis, including 40 doses of mapharsen and 16 of bismuth within a 26 week period (S. G. O. Circular Letter No. 74)

unnecessary for medical reasons since the patient is not usually ill either from his disease or as a result of treatment for it since quarantine for the protection of others (except sexual contacts) may be so brief as to be measured in hours or at most a few days and since technically these diseases are as easily treated on an ambulatory as on a hospitalized basis In both Services there are important administrative considerations which demand that the policy be continued for some infected personnel Where it is essential the period of hospital stay should be reduced to the barest possible minimum in order to conserve manpower and to minimize the punitive feature of loss of pay for loss of time A compromise between the exigencies

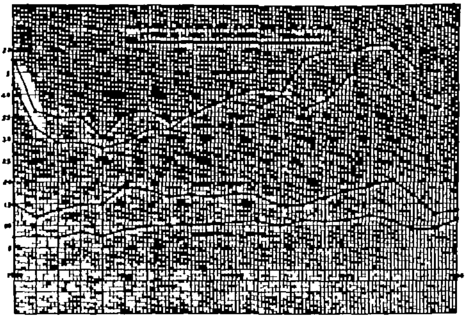


Fig. 107

of the Services on the one hand and the public health objection on the other that the policy of hospitalization adds a punitive feature which promotes concealment of disease and therefore its spread, might be reached if the length of hospital stay for the average uncomplicated case were limited to ten days or less This is a period of time adequate to cure the majority of cases of gonorrhea, to initiate treatment for syphilis and to render it noninfectious Whenever local circumstances permit the administration of treatment on an ambulatory basis the patient remaining on active duty is highly desirable most of all for conservation of manpower The Army has recently recognized these arguments in recommending (S G O Circular Letter 10.) that the period of hospitalization need rarely exceed one

week, and that thereafter most infected men may be treated with their units

Epidemiologic cooperation with civilian health agencies —A most important phase of any venereal disease control program is case-finding, i e. the discovery of unrecognized infections especially those in the early and communicable stages. Search for these unrecognized cases is especially productive among persons who have had intimate contact with infected individuals. Contact investigation thus has come to be as much a part of venereal disease control as it is in the control of other infectious diseases, such as typhoid fever or diphtheria.

The responsibility for accurate contact *reporting* is a duty of medical officers of the Armed Services. The *follow-up work* of necessity, devolves upon the civilian health authority who must trace and examine the contacts named and treat those found to be infected

Provision is made for the mutual interchange of contact information. It is of course as essential that soldiers and sailors be informed of the fact that they have been exposed to known cases of syphilis and gonorrhea as for civilians to have the benefit of similar information Problems of contact-tracing and examination are simplified for the Service medical officer who ordinarily can accomplish the desired examinations in short order with a minimum of difficulty

Quarantine in venereal disease control in Army and Navy —Within the Army and Navy medical officers need not worry about recalcitrants The restrictions placed upon infected men during the period of venereal disease communicability carry the authority of the commanding officer, and violations may be summarily dealt with by court martial.

In civilian population groups, whenever possible the persuasive approach to the individual infected with syphilis or gonorrhea is the preferable one, indeed the one repeatedly shown to be productive of the best results. There are nevertheless occasional recalcitrant individuals, usually prostitutes upon whom quarantine measures must of necessity be invoked. Quarantine a function of the health department can legally be enforced when an individual is known to be infectious and a menace to the public health. Only rarely does the law provide for compulsory diagnostic examination on the basis of suspicion alone In cooperation with State Health Departments, the Public Health Service is now operating detention hospitals for infected prostitutes found near military concentrations.

Substitutive activities —It is a well recognized epidemiologic principle that the incidence of any infectious disease is directly related to the number of exposures to infected persons, and that the core of the control program lies in reduction in the number of exposures.

Soldiers and sailors are not men apart. They are an unusually virile group of civilians thrown by the chance course of events into an environment offering limited opportunities for normal social contact with members of the opposite sex. Experience has shown that within any such group of men approximately 10–15 percent, restrained by moral esthetic or sanitary considerations, will not risk sexual exposure at all Another group of comparable size will expose themselves repeatedly Between

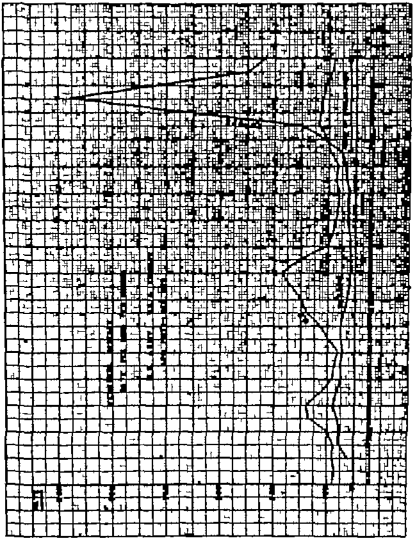


FIG. 108

these two extremes are the majority of service personnel some 70–80 per cent of the entire group who expose themselves only under special circumstances chiefly boredom or alcohol and usually not when more wholesome feminine companionship is available It is toward this last group that efforts directed at reducing the number of sexual exposures are most effective.

Recreational activities.—Boredom, strain and inability to relax, dreaded by both Army and Navy as deterrents to morale are likewise potent factors in the incidence of venereal disease The extent to which boredom may contribute to a high venereal disease rate is best illustrated by the experience of the American Expeditionary Force in Europe after World War I when for a brief time the incidence rate was more than 1000 per 1000 per year (Figure 108)

To combat these factors both Services have developed elaborate programs Organized physical exercise and conditioning form part of the regular training curriculum Another portion of the program, under the cognizance of the Special Services Section of the Army and of the Welfare and Recreation Section in the Navy, is extra-curricular and designed to fill in leisure time with on-the-post educational, athletic and recreational activities.

The perfectly normal desire of young men for the companionship of young women must be recognized and met. Here is clearly the job of civilian welfare agencies and specifically the task of the United Service Organizations—to provide opportunities for good times in good company By making available to the Service man on leave a comfortable place to sleep and eat, amusements and games and congenial, wholesome young women for conversation and for game and dance partners the U S O offers "substitutive" activities of inestimable value to morale and to venereal disease control. These facilities should be extended to troops abroad as rapidly as possible.

A somewhat different approach is provided by the Chaplains Corps of the respective Services whose appeal lies in the emphasis upon the moral aspects of clean living and clean thinking, motivated by religious teachings.

Prostitution

In attempting to reduce the number of sexual exposures the Armed Forces are confronted with the age-old problem of prostitution which provides at once the most freely available source of exposures and the greatest number of infected contacts The Medical Corps of Army and Navy are not interested in prostitution as a moral issue, but only because it constitutes the most potent source of venereal infections. Modern prostitution is now often diffused and scattered The part-time clandestine prostitute far outnumbers her more commercialized sister Moreover as the Services have discovered the prostitutes have taken a leaf from their own book and have become motorized Mobile trailer camps make hit-and-run commando-like raids into areas of service concentration on pay

days and disappear well before the infections which they engender become manifest.

It is now the expressed policy of the Federal Government through its subsidiary departments Army Navy and Federal Security Agency that prostitution be neither segregated, supervised nor tolerated, but rigidly repressed This policy is based upon sound medical and socio-economic reasoning The facts of the matter are that prostitution is not a necessary evil that segregation of prostitution increases the number of contacts of the individual carrier and thus increases the probability of infection that medical inspection of prostitutes is a thoroughly unreliable procedure repeatedly shown to be a complete failure that repression does not necessarily spread prostitution nor does it place in jeopardy the "nice" girls of the community

The Navy has had several experiences with controlled and supervised prostitution sufficient to convince all concerned of the impracticality of the method During the occupation of one town in Haiti by the Marines in 1917 segregation and inspection were tried At the beginning the venereal disease rate was 170 per thousand but at the end of the controlled experiment, which lasted nearly a year the rate had increased to 243 per thousand

Effective control of venereal diseases requires the vigorous repression of prostitution, commercial and clandestine not only in areas adjacent to military and naval concentrations but also in communities to which Service personnel may go on leave The word "repression" is carefully chosen instead of the stronger term "suppression" since experience has shown that much can be accomplished in repression whereas suppression is a Utopian and unattainable aim The compelling medical reason for repression is the minimizing of potentially infectious contacts. If segregated districts and isolated brothels are not tolerated and if flagrant solicitation on the streets in cabarets dance halls and by "trailer girls" is vigorously repressed the number of contacts which a prostitute can make in a given time period is reduced from the not unusual record of 50–75 per night to a much smaller quota and the number of men one prostitute can infect is thereby decreased

Repression of prostitution together with its subsidiaries, the madams exploiters panderers and the corrupt politicians is a civilian police function over which the Army the Navy the Public Health Service, the local Health Department and other interested groups have only indirect control Practically every community has laws against prostitution but few apply them intelligently persistently and without prejudice The Federal Government considers the effort to promote enforcement of existing statutes by the local police so important that a separate division has been created within the Federal Security Agency the Division of Social Protection whose expressed aim is toward this end

Failing to obtain the cooperation of the local police authorities the Army and Navy have recourse to two steps. One is to declare a section or even an entire community out of bounds to men in uniform and to station a cordon of military police to enforce the order This procedure has

repeatedly been shown to be effective (although it is of interest to note that the highest venereal disease rate among American forces stationed in Paris during World War I was in the Military Police! The peculiar susceptibility of Military Police to venereal infections is still demonstrable in many locations in this war) The other recourse lies in the invocation of the May Act, whereby at the discretion of the Secretary of War or Navy prostitution may be declared a Federal offense, subject to enforcement by the Federal Bureau of Investigation.

Prophylaxis

The Armed Services are concerned not only with reducing the total number of sexual exposures, but also with the number of potentially infectious exposures To this end prophylaxis is essential The ideal prophylactic should be at once effective, transportable, inexpensive and readily available This war has brought the realization that little is actually known about prophylaxis, and that additional information is urgently needed. It is known that the condom if properly used will prevent the development of lesions in areas actually covered. It is also known from animal and human experimentation and from Army and Navy clinical data that 33⅓ per cent calomel ointment will protect against syphilitic infection if locally applied in sufficient quantity within 1 to 4 hours after exposure perhaps as long as 8 hours and that cleansing with soap and water may protect if applied immediately Chemotherapeutic prophylaxis against gonorrhea (and possibly against chancroid and lymphogranuloma as well) with sulfathiazole has been tried on a limited scale by Army and Navy with apparent success.

Prophylactic treatment is available to enlisted personnel of the Army and Navy at special stations operated by trained hospital personnel and through the personal use of the condom and the prophylaxis packet. Each has its place. Where large numbers of men incur frequent exposures supervised prophylaxis in established stations when the latter are conveniently available and well advertised is preferable. Self-administered packet prophylaxis about which less factual information is available has the advantage of being readily usable immediately after exposure Under the conditions of this war it is probable that the latter method will find the wider application

Army and Navy medical officers have a unique opportunity to study the relative effectiveness of various modifications of prophylactic treatment and a considerable fund of information should shortly be available from their experience and from planned investigations now under way in various research centers.

Education

It is usual for the Army or Navy recruit to receive soon after being inducted three lectures on venereal disease one by a line officer on the military aspects of these diseases as detriments to the best interests of the Service one by the chaplain stressing moral aspects, and a third by the medical officer whose emphasis is upon prevention. That additional meas-

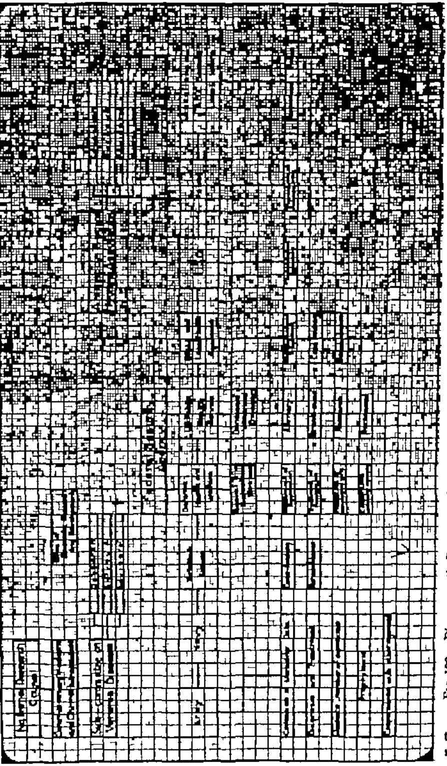


FIG. 102.—Diagrammatic Representation of Inter-relationship of Governmental and Other Agencies to Venereal Disease Control in the Present War

ures are needed has recently been demonstrated by a questionnaire survey of the insight of men attached to a Navy vessel, which revealed a startling amount of misinformation

Within recent months, both Services have implemented their educational programs with posters and motion pictures and there is a growing tendency to distribute pertinent literature in pamphlet form

The educational program however should not be confined to the enlisted soldier or sailor There is also need for well planned propaganda among line officers in authority some of whom unwittingly impede venereal disease control measures because of ignorance of facts. Medical officers likewise not infrequently require additional information as to the diagnosis and treatment of syphilis and as to the imperativeness of control procedures.

In the civilian population, educational measures should be concentrated on physicians, politicians and local governmental and police officials responsible for the enforcement of various control measures The general public and particularly the more vocal groups within it, such as influential women s clubs civic leagues, etc. can if sufficiently aware and aroused, exert considerable pressure in the right direction

The Ramifications of Military Venereal Disease Control

Venereal disease control under any conditions whether those of peace and war involves a complicated set of interlocking relationships between medical and social agencies of various types. In these days of organizational diagrams it is appropriate to illustrate the war ramifications of some of these in graphic form (Figure 109)

Punitive Measures

Since 1778 when Congress provided that any officer should be fined $10 and any enlisted man $4 who should be admitted to a hospital with a venereal disease various punitive measures have been enacted in an effort to decrease the incidence of venereal infections in the Armed Forces. Punitive measures are based upon the fallacious assumption that acquisition of venereal disease is *a priori* evidence of "misconduct" This interpretation overlooks the fact that many perhaps the majority of soldiers and sailors are guilty' of the same misconduct but are not punished or punishable because they are fortunate enough to escape infection In other words the Army and Navy are still chargeable with the point of view which stigmatizes venereal infections as sins rather than as diseases, a point of view which civilian experience has repeatedly shown promotes concealment of infection and therefore its continued and surreptitious spread. The Armed Forces would profit from the experience of society in general by the adoption of the principle that venereal disease is not controlled by punishment. It is desirable, therefore that disciplinary measures be entirely abolished by regulation wherever possible by act of Congress where necessary These include the requirement by regulation of loss of pay for loss of time the non-required but tacitly practiced demotion of

infected non-commissioned officers restrictions against promotion in non-commissioned or commissioned rank because of a previous history of syphilis or gonorrhea and the ridiculous mix-up which denies a qualified applicant for commission from civilian life if his medical history includes well treated even cured syphilis though leaving him eligible for enlisted service through induction In the Navy regulations at present in effect provide that anyone with syphilis or a history of it may not become a commissioned officer may not attend the United States Naval Academy or enter the Air Corps Submarine Service or be a deep sea diver! It is difficult to see how these measures contribute toward reducing the incidence of venereal disease but they do promote concealment of disease and thus actually contribute to its spread. Further in these days of urgent need of men the Services deny themselves unnecessarily of valuable personnel

Responsibility of unit commanders —In this war the responsibility of the unit commander is defined in War Department Circular No 249 (December 5 1941) 'The prevention and control of venereal diseases is the responsibility of the unit commander and for the personal performance of that duty he will be held strictly accountable. Unless extenuating circumstances exist, a high incidence of venereal disease in a command shall be regarded as a lack of efficiency on the part of the commander concerned. Commanders of units having a low incidence shall receive full credit for their accomplishment. Unit commanders are required to explain any unusual increase in the venereal disease rate of their commands and the necessity of periodic reports keeps the problem before them

It is of course eminently desirable to obtain the unqualified support of the commanding officer of each military and naval unit since in them is vested the authority necessary for many of the control procedures On the other hand it would be difficult to delineate a rate over which one commander would be commended and under which another would be reprimanded. A command in certain Southern states or foreign stations where the civilian rate is high could hardly be expected to compete with another in New England If unit commanders are to be held accountable one would expect the account to be based upon the trend of incidence within his command.

The Venereal Disease Control Officer in This War

Prior to Pearl Harbor both Army and Navy had established Subdivisions of Venereal Disease Control under the Divisions of Preventive Medicine in the offices of the respective Surgeons General but until the actual outbreak of war the personnel of these Subdivisions and their duties were largely nominal Early in 1942 however both Services rapidly expanded their venereal disease control effort. More than 150 Army and 60 Navy medical officers are now (November 1942) assigned to such duty Many of these officers have had expert training in civilian life many others have undergone a two month period of post-graduate training in the public health and clinical aspects of the subject

In the Army venereal disease control officers are authorized in each Service Command and at each troop concentration of 20 000 men or more

(in the continental United States) and a few have already gone abroad with various Expeditionary Forces The Navy has similar officers in each Naval District, and in many areas of large naval concentration but as yet is inadequately represented abroad.

The duties of the venereal disease control officer in each Service include many of the measures described above the gathering of accurate statistics primarily in order to define the areas where control activities are most needed cooperation with civilian agencies in the epidemiologic approach to case finding cooperation with Service and civilian agencies in substitutive and recreational activities cooperation with law enforcement officials in the repression of prostitution cooperation with the Chaplains Corps cooperation with the Provost Marshal in police control of men in leave areas supervision of prophylaxis and education, not only of enlisted personnel but also of line and medical officers Some venereal disease control officers depending on their stations, participate in or direct the professional care of infected patients or act in a consultant capacity in this respect.

Certain important phases of the venereal disease problem as a whole are still outside the province of the Subdivisions of Venereal Disease Control These include responsibility for the formulation of policies and general supervisory control of their execution in the following respects (1) the professional care of infected persons both as to diagnosis and treatment (2) the acceptance by the Services in enlisted or commissioned rank, of persons previously infected in civil life (3) the suitability of infected personnel for special duty e.g flying Could these be centralized in the hands of the specially trained and capable officers attached to the venereal disease control group they would be more competently performed and in the second item at least, some order might grow out of what now appears chaotic

For the aid of venereal disease control officers and indeed of all medical officers (since the desired reduction in incidence rates is a part of the job of all) there are herewith appended as Tables 127 and 128, lists of important Army and Navy orders, regulations circular letters, and documents relating to venereal diseases and their control.

The next major step toward a lowered incidence rate is the rapid extension of venereal disease control effort with our troops overseas It cannot be too strongly urged that the higher rates and therefore the greater need for trained venereal disease control officers, is likely to come from troops on garrison duty abroad, especially in tropical areas

If this Army equals the record of the American Expeditionary Force in France of halving pre-war incidence rates, it will have performed an achievement for which the United States may well be proud and grateful. Every soldier and sailor in whom infection is prevented contributes his full might toward victory

TABLE 127

ARMY REGULATIONS AND LETTERS RELATING TO V D

War Department Letters

Date	Subject
9-19-40	Cooperation of the United States Public Health Service in extra-military sanitation.
12-16-40	Control of the use of intoxicating beverages by military personnel and the improvement of moral conditions in the vicinity of camps and stations.
1 13-41	Cooperation with the United States Public Health Service in the control of venereal diseases.
6-11-41	Corps Area Consolidated Venereal Reports.
8- 2-41	Cooperation with the Public Health Service in reporting laxness of law enforcement in connection with the control of venereal diseases.
8- 9-41	Education in sex hygiene and the venereal diseases.
10- 2-41	Establishment of the Division of Social Protection by the Federal Security Agency
10-10-41	Prohibition of prostitution within reasonable distance of military establishments.
10-17-41	Control of venereal diseases.
1 19-42	Control of venereal diseases.
2- 6-42	Venereal Disease Control officers.
2-14-42	Reporting of sources of venereal diseases.
5-29-42	Transfer of soldiers with venereal diseases.
8-27-42	Fever therapy in the treatment of gonorrhea.
9- 1-42	Equipment of camps to be used by defense health and welfare service.

War Department S G O Circular Letters

Date	Subject
1 2-41	C L. No. 1 Section IV Professional
2 12-41	C L. No. 10. Serologic tests for syphilis.
5-28-41	C.L. No. 50 Cooperation with state health departments in reporting of venereal diseases.
4-23-42	C.L. (unnumbered) Waiver of Physical Defects for Limited Service Officers.
4-30-42	C.L. No. 39. Serologic tests for syphilis.
7 25-42	C.L. No. 74. Diagnosis and Treatment of venereal diseases.
7 27-42	C. L. No. 76. Discontinuance of reports and records.
7-31-42	C.L. No. 80. Individual venereal disease prophylactic packets.
8-18-42	C.L. No. 86. Fever Therapy in the treatment of gonorrhea.
9-11-42	C.L. No. 105. Treatment of syphilis by unit medical officers.
9-21-42	Induction of men with uncomplicated gonorrhea.
11 19-42	Venereal Disease Control Officer

War Department Bulletin

Date	Subject
8- 8-41	No. 23. Section I—Act of Congress. Limitation of Prostitution near Army establishments.

War Department—Army Regulations

Date	*A R No.*	*Subject*
4-21 23	40- 270	The Medical Inspector
5-29-23	40- 105	Standards of Physical Examination for entrance into the regular Army National Guard, and Organized Reserve
6- 6-24	40-1030	Register of Sick and wounded.
2-20-25	615- 250	Physical inspections—Enlisted men
11 15-32	40- 275	Sanitary Reports
11 16-33	35-1440	Loss of Pay during Absence due to diseases resulting from misconduct.

11 23-33	345- 415	Daily sick report.
12-31-34	40-1080	Current statistical reports, tables and charts.
4- 1-40	40- 110	Standard physical examinations for flying
9-10-40	40- 100	Standards of miscellaneous physical examinations (including annual physical examination of officers and others, and physical examinations for flying)
9-15-42	40- 210	Prevention and control of Communicable Diseases of man.
10-14-42	40- 105	Standards of physical examination for commission.
11 16-42	40- 100	Standard for Miscellaneous Physical Examination.

War Department Circulars

Date	*No.*	*Subject*
2 1-40	14	Change in A.R. 40-235 (disciplinary action)
11-23-40	136	Pay of enlisted men (7th grade) under the Selective Training & Service Act of 1940.
4- 1-41	53	Changes in A.R. 40-235 (movie films can be substituted for lectures)
4-16-41	71	Routing of reports pertaining to sick and wounded.
8-16-41	170	Section II. Prohibition of prostitution within a reasonable distance of military establishments.
12- 5-41	249	Venereal disease.
12-16-41	258	Section II. Policy regarding declaration of certain places as "off limits."
2-23-42	53	Section II Venereal disease prevention.
5-30-42	166	Section IV Monthly venereal disease statistical report.
8-26-42	285	Section I. Monthly venereal disease statistical report.
11 24-42	380	Disciplinary control of military and naval personnel.

Miscellaneous

3-20-42	War Department letter to governors of all states, signed by the Secretary of War Henry L. Stimson re suppression of venereal disease.
3-15-42	MR 1-9 Standards of physical examination during mobilization.
9- 6-42	Weekly statistical report, Form 86ab MD (radiogram from Office of the Surgeon General)

TABLE 128

NAVY PUBLICATIONS RELATING TO VENEREAL DISEASES CONTROL

Navy Regulations

N R. 1135	Suggestions to commanding officer re prevention of disease
N R. 1136	Concealment of disease
N R. 1142	Transfer of patients with venereal infections
N R. 1196	Disease or injury due to misconduct

Manual of Medical Department

M.M.D	Chapt. 6. *General Duties of Medical Officers*
701	Medical officers responsible for prevention and control of disease
702	(c) Examinations for detection of concealed disease
704	(b) Instruction of personnel re Venereal Disease
707	Cooperation with other agencies, including U S.P.H.S.
M.M D	Chapt. 11 *Physical Examinations*
1506	Serologic tests for syphilis
1508	Standards for applicants for enlistment or commission
M M.D	Chapt. 14. *Health Records*
2287	Venereal disease patients admitted to sick list, if for record only
2350	The Syphilitic Abstract (*sic*)
M.M.D	Chapt. 10. *Special Activities*
1281	Venereal disease in submarine personnel
M.M D	Chapt. 15. *Nomenclature of Diseases and Injuries*
2408	Venereal Diseases, Class XII
M M D	Chapt. 16. *Misconduct status*
M.M.D	Chapt. 17 *Preventive Medicine and Sanitation*
2702	Calculation of annual rates
2703	Form A. Report (cases of syphilis and arsenical reactions)
2712	Intelligence reports. Sanitary condition of ports visited
M.M.D	Chapt. 23. *Reports and Returns*
3411	Form A. Report of cases of syphilis and arsenical reactions
M.M D	Appendix A. *Nomenclature of Diseases and Injuries* A. Class XII. Venereal diseases
M M.D	Appendix B Bureau Circular Letter Y 1 Control of communicable diseases, including gonorrhea, syphilis, and lymphogranuloma venereum
M.M.D	Appendix D Bureau Circular Letter Y Form A—Instructions regarding
M.M D	Changes for Chapt. 11 (2-1-41)
1548	History of syphilis disqualifying for flying

Navy Department General Orders

5-13-35	No. 14. Prevention and Control of Venereal Disease
5-15-35	No. 20 Forfeiture of pay for absence from duty
10-13-41	No. 156. Control of prostitution in areas adjacent to naval activities

Letters Secretary of the Navy

3-16-42	Navy Department letters to governors of all the States requesting co-operation in V D control
3-21-42	NAV 147 RI P13-6(37) Policy on repression of prostitution
7 19-40	P3-1 (400226)B Ca DC Venereal Disease—Preventive and Punitive Measures.
2 27-41	ALNAV #18 Repression of prostitution.

Letters Chief of the Bureau of Medicine and Surgery

7-30-40	P3-3/ET12 (021) Probable source of venereal infection of naval personnel, reporting of to civilian health authorities

11 13-41 A3-3/EN10(112) Y-ec Place of exposure to venereal disease, reporting of—(From Letter No. 14)
6-22-42 P2-5/P3 (111-38) Y-ems Presumptive Kahn tests—Adoption of
9-10-42 P3-1/P3-2 (061) Venereal Disease Prophylaxis

Joint Letters Bureau of Medicine and Surgery and Bureau of Navigation (Now Bureau of Personnel)

4-25-41 {NAV 147 RNC P2-1 (85) Control of Venereal Disease
{P2-2/AT12 (021)-40)
4- 1-42 {NAV 147 RI P16-3/VD (1550) Employment of Venereal Disease Control Officers
{P3-2/ET12 (021-40)

Miscellaneous

Naval Courts and Boards. Section 710. Definition of misconduct
10- 8-25 Comp. Gen. 229 Venereal disease infections misconduct unless proved otherwise

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AUTHOR INDEX

The numbers in roman type indicate reference to the designated author in the body of the text those numbers in *italics* refer to the citation of the author in a bibliography

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